#51

The opinion in support of the decision being entered today is not binding precedent of the Board.

Paper No. 262

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

ROBERT C. **ROSE**,
WILLIAM BONNEZ and RICHARD C. REICHMAN,
Junior Party,
(Application 08/207,309)

v.

C. RICHARD **SCHLEGEL** and A. BENNETT JENSON,
Senior Party
(Application 08/216,506).

Patent Interference 104,772

DOUGLAS R. **LOWY**,
JOHN T. SCHILLER and REINHARD KIRNBAUER,
Junior Party,
(Application 08/484,181)

v.

C. RICHARD **SCHLEGEL** and A. BENNETT JENSON,
Senior Party
(Application 08/216,506).

Patent Interference 104,774

IAN **FRAZER** and JIAN ZHOU,
Junior Party
(Application 08/185,928)

v.

C. RICHARD **SCHLEGEL** and A. BENNETT JENSON,
Senior Party
(Application 08/216,506).

Patent Interference 104,776

Before: McKELVEY, Senior Administrative Patent Judge, LANE, TIERNEY, MOORE, and NAGUMO, Administrative Patent Judges.

TIERNEY, Administrative Patent Judge.

DECISION — SCHLEGEL PRIORITY DATE — BD.R. 125(a)

Initial observation

The subject matter involved in six related, but separate, Interferences 104,771 through 104,776 involves complicated biotechnology. At the outset of each interferences, the parties were advised that it would be helpful if presentations could be made using "plain English" (Paper 3). Instead, counsel for the parties have all elected to present their respective cases (both testimony and briefs) in large measure using "biotechese". We have not been able to find that any attempt was made by the parties to present a useful glossary of terms referenced directly in the briefs. We have also not been able to find any attempt to have a witness explain the technology in more basic terms. We have not been able to find in a brief a "plain English" explanation of the subject matter involved. In short, there was no attempt to educate the board in simple terms on the technology involved. We do not know why the parties basically chose to ignore Paper 3.

If the kind of exposition we are asking for were easy to write, we probably would not need to ask parties to read and comply with ¶ 43 ("Reliance on scientific tests and data") of the Standing Order (Paper 2). The study and practical applications of complex subjects leads, necessarily, to sophisticated, technical concepts, which tend to be expressed in sophisticated, technical language. Concepts that have been reduced to things that are "patentable subject matter," however, can usually be explained to an audience in terms that explain the concepts while avoiding the technical jargon. Such explanations are not "dumbing down" the subject matter. The lack of a plain English technical background has made the case difficult to decide. Examples follow.

Rose

> The Rose claims require that L1 protein in virus-like particles be recognized by sera obtained from (human) patients exposed to certain viruses. What, exactly, are "sera"? What is in them as a result of exposure to a virus and what else might be present? What tests are done to see if the L1 protein is "recognized"? What does the recognition imply about the shape of the L1 protein, and why?

Lowy

> The Lowy claims call for capsids or virus-like particles capable of inducing high-titer neutralizing antibodies. What is a neutralizing antibody? How are titers measured in the laboratory, and when is a titer a "high titer"? How does one determine that an antibody is neutralizing?

Schlegel

The Schlegel claims call for L1 protein that "exhibits the same conformation" as the L1 protein on the surface of an intact human papillomvirus. Many of its proofs involve a certain kind of "ELISA" measurement. What is actually measured? What is the significance of what is measured?

Frazer

Frazer, due to the nature of its case, does not offer proofs for priority based on laboratory notebooks or the outcome of particular experiments. But its case requires that we understand the descriptions in its specifications and printed publications of the results of recombinant DNA technology, the production of proteins, and the assembly of proteins into particles resembling viruses.

A number of questions arose as we considered the laboratory experiments, measurements, and technical arguments on which the parties relied to prove conception or actual reduction to practice. How was the experiment done? What was actually measured? How reliable is the measurement? What controls ought to be done? Why? What is the level of the signal compared to the noise? How reproducible is the assay? How do the measurements relate to the conclusions the moving party would have us draw from its experiments? Why is the movant's proposed explanation the most likely explanation? What else could have led to the same result? These are the types of questions that ¶ 43 of the Standing Order indicates should be explained. We often found ourselves asking these questions as we sought to resolve the issue of priority in this interference. Seldom, however, could we find a simple, straightforward explanation in the briefing or in the record. Perhaps the parties assumed--erroneously--that we knew all about the experiments. What is absolutely plain is that all parties simply did not comply with the provisions of ¶ 43 of the Standing Order (Paper 2, page 30).

As a result, we have spent a good amount of time searching the record for the teachings we requested in ¶ 43 of the Standing Order. We have spent additional time assuring ourselves that our understanding, expressed in plain English, is accurate. We have attempted to summarize the major features of the involved technology for the general reader in Appendix I, which is attached to this decision. We remain somewhat nonplused that the parties would provide so little guidance to the technical foundations of their cases.

As indicated during oral argument during the priority phase, we had hoped to have final decisions entered in these six interference on or before 15 August 2005. Instead, final decisions are being entered about a month later. The "delay" in entering final decisions in large measure can be attributed to the lack of a "technical education" in "plain English" by each of the parties.

In future cases, our hope is that parties take the time to educate the board in "plain English" on the nature of the technology involved in an interference.

I. Introduction

This is a decision on Schlegel's priority date. Oral arguments in related interferences 104,771 through 104,776 were held on 30 June 2005 before a court reporter. Michael Goldman, Esq., argued for Rose. Brent Babcock, Esq., and Nancy Vensko, Esq., argued for Lowy. Beth Borrous, Esq., argued for Frazer. Elliot Olstein, Esq., argued for Schlegel.

Schlegel is the senior party in each of the three interferences in which it is present. Specifically, Schlegel has been accorded a constructive reduction to practice date of June 25, 1992 in Interference Nos. 104,772, 104,774 and 104,776. The junior parties have been accorded constructive reduction to practice dates as follows:

Rose, Interference No. 104,772: March 9, 1993

Lowy, Interference No. 104,774: September 3, 1992

Frazer, Interference No. 104,776: July 20, 1992

As discussed in the various opinions on priority, filed concurrently herewith, neither Rose, Lowy nor Frazer has demonstrated by a preponderance of the evidence that they are entitled to an actual reduction to practice date prior to their constructive reduction to practice date. Further, neither Rose, Lowy nor Frazer has established conception plus reasonable diligence from a time prior to Schlegel's constructive reduction to practice date of June 25, 1992 to a reduction to practice or that Schlegel derived the invention from another. Accordingly, Schlegel prevails on the question of priority in Interferences 104,772, 104,774 and 104,776 against Rose, Lowy and Frazer based upon its earlier constructive reduction to practice date. As an alternative basis for prevailing on priority of invention as to Rose, Interference 104,772, we have reviewed Schlegel's case on priority and determined that Schlegel has established that it conceived and reduced the invention to practice prior to its constructive reduction to practice date and that it was diligent in its efforts to reduce the invention to practice from the date of its conception until the date of its actual reduction to practice. Schlegel's earlier conception, reduction to practice and diligence for Interference 104,772 is discussed below. We note that the counts in the '772 and '774 interferences contain overlapping subject matter, e.g., Schlegel claim 64, and that Schlegel's principal case for priority is generally the same as those in both the '772 and '774 interferences.

II. Summary of the Opinion

Schlegel alleges that it conceived of the invention and diligently reduced it to practice prior to Rose. In particular, Schlegel focuses on that portion of the count that includes Schlegel claims 1 and 64 and argues that proof of a conception or actual reduction to practice of Schlegel

claim 1 is a proof of conception or reduction to practice of Schlegel claim 64 and vice versa. We focus our review of Schlegel's case on its priority allegations with respect to Schlegel's claim 64.

Schlegel alleges at least seven distinct dates of conception, five different dates of actual reduction to practice and diligence spanning the time of its earliest alleged conception, October 3, 1990, until its constructive reduction to practice on June 25, 1992. Rose concedes that Schlegel conceived of an embodiment within the scope of the count on March 16, 1992, but denies that Schlegel actually reduced to practice the subject matter of the count and denies that Schlegel exercised diligence from its earliest conception to its constructive reduction to practice.

We have reviewed Schlegel's alleged conceptions and conclude that Schlegel conceived of an embodiment falling within the scope of the count on or about December 3, 1991, the date of its third alleged actual reduction to practice. Further, we have reviewed Schlegel's alleged five actual reductions to practice and hold that the first (October 23, 1991), the second (November 3, 1991) and fifth (March 18, 1992) alleged reductions to practice did not involve "isolating" recombinant HPV ("human papillomavirus") L1 protein, a limitation required by Schlegel claims 1 and 64. As for the third alleged reduction to practice, Schlegel failed to conduct sufficient testing to demonstrate that its HPV-1 L1 protein specifically binds to conformational antibodies which react with an L1 protein expressed on the surface of an intact HPV virion. Schlegel's alleged fourth reduction to practice on March 16, 1992, provided sufficient testing and is held to be an actual reduction to practice of an embodiment within the scope of the count. Schlegel presents arguments and evidence that Dr. Ghim, working under the direction of the inventors, was reasonably diligent in her efforts to reduce an embodiment to practice between the dates of its conception no earlier than December 3, 1991 to its actual reduction to practice date March 16, 1992. Rose does not oppose Schlegel's allegations of diligence for these dates. Accordingly, we hold that Schlegel conceived of the invention on

December 3, 1991, reduced it to practice on March 16, 1992 and find that Schlegel was reasonably diligent in its efforts to reduce an embodiment of the count to practice from the date of its conception to the date of its actual reduction to practice.

III. Previous Decisions in the Interference

At the outset, we reaffirm our previous findings of fact and conclusions of law made in this interference to the extent they are consistent with this decision. Any previous findings or conclusions that are inconsistent with this opinion are vacated.

IV. Findings of Fact

Evidence presented in a separate or even a related interference is not part of the present interference record. Unless otherwise authorized by an Administrative Patent Judge, relied upon evidence must be offered into the present interference record. Similarly, arguments raised in a separate or related interference may not be "incorporated by reference" into the present interference. Accordingly, this interference has been decided based upon the arguments and evidence of record as presented by the parties in this interference.

The record supports, by a preponderance of the evidence, the following findings:

A. Previous Findings

1. Real Parties in Interest

a. Junior Party Rose

1. Rose's real party in interest is the University of Rochester and Strong Memorial Hospital. (Decision on Preliminary Motions, Paper No. 60, ¶ 14). MedImmune, Inc. and SmithKline Beecham PLC are licensees. (*Id.*).

b. Senior Party Schlegel

2. Schlegel's real party in interest is the Georgetown University School of Medicine. (*Id.* at ¶ 20). MedImmune, Inc. and SmithKline Beecham PLC are licensees. (*Id.*).

2. Accorded Priority Benefit

a. Junior Party Rose

3. Rose's involved U.S. Application No. 08/207,309 ("Rose '309") was filed March 7, 1994.

4. Rose '309 is said to be a continuation-in-part application of U.S. Application 08/028,517 ("Rose '517"), which was filed March 9, 1993.

5. For the purpose of 35 U.S.C. §102(g) priority, Rose was accorded benefit of its '517 application and thus Rose's earliest constructive reduction to practice date is **March 9, 1993**.

6. The named inventors of the involved 309 application are Robert C. Rose, William Bonnez, and Richard C. Reichman.

b. Senior Party Schlegel

7. Schlegel's involved U.S. Application No. 08/216,506 ("Schlegel '506") was filed March 22, 1994.

8. Schlegel '506 is said to be a continuation of U.S. Application No. 07/903,109 ("Schlegel '109") application, which was filed June 25, 1992.

9. For the purpose of 35 U.S.C. §102(g) priority, Schlegel was accorded benefit of its '109 application and thus Schlegel's earliest constructive reduction to practice date is **June 25, 1992**.

10. The named inventors of Schlegel's involved '506 application are C. Richard Schlegel and A. Bennett Jenson.

3. The Count

11. Count 1 is the sole count in the interference and reads as follows:

> A composition of matter according to any of claims 42, 43 or 65 of Rose or a method according to any of claims 44, 56 or 71 of Rose,
>
> or
>
> a composition of matter according to any of claims 1, 12, 50 or 64 of Schlegel or a method according to any of claims 19, 53 or 55 of Schlegel.

(Redeclaration, Paper No. 61, p. 2).

12. The patentable claims of the parties are as follows:

> Rose '309: 35-37, 41-45, 48, 50, 52-57, 59, 61-65, 67-72, 75-77, 79-89 and 91
> Schlegel '506: 1–3, 12–14, 16, 19, 23–25, 46, 47, 50, 52, 53, 55–60, 62, and 64.

(*Id.*).

13. The parties claims that correspond to Count 1 are as follows:

> Rose '309: 35-37, 41-45, 48, 50, 52-57, 59, 61-65, 67-72, 75-77, 79-89 and 91
> Schlegel '506: 1–3, 12–14, 16, 19, 23–25, 46, 47, 50, 52, 53, 55–60, 62, and 64.

(*Id.*).

14. The parties claims that do not correspond to Count 1 are as follows:

Rose '309: None
Schlegel '506: None

(*Id.*).

a. Relevant Schlegel Claims

15. Schlegel and Rose attempt to demonstrate priority of invention by submitting proofs that are said to fall within the scope of at least Schlegel '506 claims 1 and 64, which read as follows:

> 1. An isolated recombinantly produced human papillomavirus (PV) L1 protein, wherein said protein reproduces the antigenicity and exhibits the same conformation as an L1 major capsid protein expressed on the surface of intact human papillomavirus virions.
>
> 64. An isolated recombinantly produced human papillomavirus (HPV) L1 protein, comprising a protein which specifically binds to conformational antibodies which react with an L1 protein expressed on the surface of an intact HPV virion.

(Schlegel Principal Brief on the Issue of Priority, Paper No. 74, pages 4-5, Appendix 1; Rose Principal Brief on the Issue of Priority, Paper No. 72, p. 26).

b. Relevant Rose Claims

16. Rose also attempts to demonstrate priority of invention by submitting proofs that are said to fall within the scope of Rose '309 claims 43, 44, 56 and 71, which read as follows:

> 43. An isolated non-infectious, recombinant human papillomavirus virus-like particle or capsomere produced according to the method comprising: infecting a cell with a recombinant expression vector containing a human papillomavirus type-6 L1 capsid protein coding sequence or a human papillomavirus type-11 L1 capsid protein coding sequence under conditions facilitating expression of said L1 capsid protein, thereby producing a non-infectious human papillomavirus virus-like particle or capsomere comprising a human papillomavirus type-6 L1 capsid protein sequence or a human papillomavirus type-11 L1 capsid protein sequence, which is conformationally correct and is recognized by antibodies present in sera

obtained from human papillomavirus type-6 infected human patients or human papillomavirus type-11 infected human patients, respectively, and isolating said particle.

44. A method of producing an isolated non-infectious human papillomavirus virus-like particle or capsomere in a cell comprising: transfecting a cell with a recombinant expression vector containing a human papillomavirus type-6 capsid protein coding sequence or a human papillomavirus type-11 capsid protein coding sequence under conditions facilitating expression of said capsid protein, thereby producing a non-infectious papillomavirus virus-like particle or capsomere comprising a human papillomavirus type-6 L1 capsid protein sequence or a human papillomavirus type-11 L1 capsid protein sequence, which is conformationally correct and is recognized by antibodies present in sera obtained from human papillomavirus type-6 infected patients or human papillomavirus type-11 infected patients, respectively, and isolating said particle.

56. A method of producing an isolated non-infectious human papillomavirus virus-like particle or capsomere in an insect cell comprising: cloning a human papillomavirus L1 capsid protein coding sequence selected from the group consisting of a human papillomavirus type-6 L1 capsid protein coding sequence and a human papillomavirus type-11 L1 capsid protein coding sequence into a baculovirus transfer vector; co-transfecting insect cells with said baculovirus transfer vector and *Autographa californica* nuclear polyhedrosis virus genomic DNA; recovering recombinant baculoviruses; and infecting said insect cells with said recombinant baculoviruses under conditions facilitating expression of the capsid protein, thereby producing a non-infectious papillomavirus virus-like particle or capsomere comprising a human papillomavirus type-6 L1 capsid protein or a human papillomavirus type-11 L1 capsid protein, which is conformationally correct and is recognized by antibodies present in sera obtained from human papillomavirus type-6 infected patients or human papillomavirus type-11 infected patients, respectively, and isolating said particle.

71. A method of producing an isolated non-infectious human papillomavirus virus-like particle or capsomere in a cell comprising: transfecting a cell with a recombinant expression vector containing a human papillomavirus capsid protein coding sequence under conditions facilitating expression of said capsid protein, thereby producing a non-infectious papillomavirus virus-like particle or capsomere comprising an L1 capsid protein for the human papillomavirus, which is conformationally correct and is recognized by antibodies present in sera obtained from patients infected with the human papillomavirus.

(See, e.g., Paper No. 72, p. 38).

B. Additional Findings

1. Overview of Schlegel's Case

a. People Involved in Schlegel's Alleged Conception and Reductions to Practice

17. Schlegel alleges that, prior to October 1990, the inventors, Dr. Schlegel and Dr. Jenson, discussed the production of a recombinant L1 protein of papillomavirus that had conformational epitopes. (Paper No. 74, p. 11).

18. Schlegel alleges that based upon their discussions, Dr. Schlegel and Dr. Jenson "decided to initiate work with respect to such recombinant production in the laboratory of Dr. Jenson." (*Id.*).

19. Dr. Ghim was a post-doctoral fellow working in Dr. Jenson's laboratory. (*Id.* at 11-12).

20. According to Schlegel, Dr. Ghim "performed the experimental work to recombinantly express such an L1 protein and to test for conformational epitopes." (*Id.* at 12).

21. Schlegel alleges that Dr. Ghim reduced the invention to practice prior to the filing of Schlegel's '506 application on June 25, 1992. (Paper No. 74).

22. Dr. Anthony Wlazlo testifies that he worked at Georgetown University as a research assistant from August 1990 through June 1997. (SX 2074, ¶ 1).

23. Dr. Wlazlo testifies that from at least August 1990 through June 1992 he worked, along with Dr. Ghim, in Dr. Jenson's laboratory.

24. Schlegel alleges that Mr. Wlazlo corroborates Dr. Ghim's work. (Paper No. 74, pages 9 and 15).

I. The Inventor's Backgrounds

25. Dr. Jenson's curriculum vitae identifies Dr. Jenson as having received an M.D. degree in 1967 from Baylor College of Medicine. Of note, Dr. Jenson was an Associate Professor of Pathology at Georgetown University from 1981-1989 and a full Professor of Pathology at Georgetown from 1989-2000. Dr. Jenson's curriculum vitae also lists him as a co-organizer of the "Sixth International Papillomavirus Workshop" held at Georgetown University on June 14-18, 1987. (SX 2067).

26. Dr. Schlegel's curriculum vitae lists him as having received a M.D./Ph.D. from Northwestern University Medical School in 1975. Dr. Schlegel was a Clinical Associate Professor in the Department of Pathology at Georgetown University between 1988 to 1990, an Associate Professor between 1990-1992 and a Professor from 1992 to present. Of note, from 1989 to 1992, Dr. Schlegel was Chairman of the "Role of Human Papillomavirus Detection Tests Committee," for the International Society for the Study of Vulvar Disease. (SX 2067).

ii. Dr. Ghim and Dr. Wlazlo's Backgrounds

27. Dr. Ghim's curriculum vitae lists her as having received a Ph.D. in Microbiology from Lyon I University in 1989. Additionally, the curriculum vitae identifies Dr. Ghim as a Postdoctoral Fellow in the Department of Pathology at Georgetown University from 1989 to 1992, a Research Associate from 1992 to 1993, an Assistant Professor at Georgetown University from 1993 to 2000. (SX 2071).

28. Dr. Ghim's curriculum vitae identifies her as a coauthor of three publications relating to papillomaviruses during the 1989 to 1992 time frame. The publications are as follows:

i. Jenson A.B., P. Lim, S. Ghim. L. Cowsert, C. Olson, Y.Y. Lim., C. Farquhar, and W. Pilacinski. Identification of linear epitopes of the BPV-1[1] L1 protein recognized by sera of infected or immunized animals. Pathobiology 59:396-403, 1991.

ii. Ghim S., N.D. Christensen, J. W. Kreider and A.B. Jenson. Comparison of neutralization of BPV-1 infection of C127 cells and bovine fetal skin xenografts. Int. J. Cancer. 49:285-289, 1991.

iii. Ghim S., A.B. Jenson and R. Schlegel. HPV1 L1 protein expressed in COS cells displays conformational epitopes found previously only on intact virions. Virology 190:548-552, 1992.

(SX 2071).

29. Dr. Wlazlo's curriculum vitae lists him as having received a B.S. in Microbiology from the University of Minnesota in 1989 and a Ph.D. in Experimental Pathology from Georgetown University in 1997. Dr. Wlazlo's curriculum vitae states that from January 1990 to June 1997,

[1]BPV is an abbreviation for bovine papillomavirus.

Dr. Wlazlo was a Research Assistant in the Department of Pathology at Georgetown University. (SX 2075).

b. Experts Testifying in the Interference

30. Dr. Steinberg is an expert witness testifying on behalf of Schlegel. (See, e.g., SX 2088).

31. Dr. Steinberg received her Ph.D. in Microbiology from the State University of New York at Stony Brook in 1976. Dr. Steinberg testifies that she has published more than 87 papers on papillomaviruses, and has organized an international conference on papillomaviruses and currently serves as Secretary of the International Papillomavirus Society. (Declaration of Dr. Steinberg, SX 2001).

32. Dr. Sapp is an expert witness testifying on behalf of Rose. (See, e.g., RX 4222).

33. Dr. Sapp testifies that he holds M.S. and Ph.D. degrees in Biology from the University of Konstanz in Konstanz, Germany. According to Dr. Sapp, he has spent the last fourteen (14) years researching papillomaviruses and the development of vaccines for them. Dr. Sapp testifies that he has authored or coauthored over 44 peer-reviewed publications relating to papillomaviruses. (RX 4141, ¶¶ 1-6).

34. Both Dr. Steinberg and Dr. Sapp are qualified to testify as to the understanding of one of ordinary skill in the art at the relevant dates in this interference.

c. Drs. Schlegel and Jenson's Discussions

35. Dr. Jenson testifies that he and Dr. Schlegel "had numerous discussions prior to October 1990 with respect to working together to develop one or more products that could be used as a diagnostic and/or vaccine for papillomavirus." (SX 2066, ¶ 2).

36. Dr. Schlegel testifies that:

> Prior to October 1990, Dr. Jenson and I decided to work jointly on a project that would produce an L1 protein of papillomavirus by recombinant techniques available in the art, preferably in a form that was not fused to other proteins, which recombinant L1 protein would be recovered as a protein separate and distinct from an intact virion but which would have conformational epitopes of the L1 protein of an intact virion, whereby such recombinant L1 protein reproduced the antigenicity and had the same conformation of L1 protein on intact virions.

(SX 2068, ¶ 4).

37. Dr. Jenson and Dr. Schlegel testify that they decided that work would be performed in Dr. Jenson's laboratory for producing recombinant L1 protein and confirming that it possessed the conformational epitopes present on intact virions. (SX 2066, ¶ 5, SX 2068, ¶ 6).

38. Dr. Schlegel testifies that:

> Dr. Shin-Je Ghim would be the person in Dr. Jenson's laboratory who would be performing the experiments with respect to recombinant production of L1 proteins and testing thereof, in vitro, for the purpose of determining the presence of relevant epitopes.

(SX 2068, ¶ 8).

39. Both Dr. Schlegel and Dr. Jenson testify that they met on a one-on-one basis on average of once a week and discussed the work that was being conducted in Dr. Jenson's laboratory with respect to obtaining and testing empty BPV capsids, intact BPV virions and recombinant L1 protein of a papillomavirus. (SX 2066, ¶ 10, SX 2068, ¶ 9).

40. Dr. Jenson testifies that he met on average about once a week with Dr. Ghim to discuss her obtaining and testing of both empty BPV capsids, intact BPV virions and recombinant L1 protein of a papillomavirus. (SX 2066, ¶ 10).

41. Dr. Schlegel testifies that he was present at laboratory meetings with Dr. Jenson and Dr. Ghim where they would discuss the work that was performed on the recombinant L1 project and analyze experimental results. (SX 2068, ¶ 10).

d. Initial Work Regarding HPV-1 L1

42. Dr. Ghim testifies that on October 3, 1990 she began work on the project to express full length and truncated HPV-1 L1 proteins. Specifically, Dr. Ghim states that she outlined the procedure to express full length and truncated HPV-1 L1 proteins in the pKK223-3 expression vector in *E. coli*. (SX 2073, ¶ 11).

43. Bates Stamp Page 1658 in notebook SX 2083 is dated October 3, 1990 and contains notations concerning a plan for obtaining truncated L1 protein. (SX 2083).

44. Dr. Ghim testifies that Schlegel Exhibits SX 2079-2084 are "true and accurate copies of pages from my laboratory notebooks" and that the notations contained therein were prepared by her on or about the time that she performed the research and work on the project. (SX 2070, ¶ 5; SX 2073, ¶ 8).

45. Dr. Jenson testifies he is familiar with Dr. Ghim's handwriting.

46. Dr. Jenson testifies that exhibits SX 2079 through 2084 are notebook pages taken from Dr. Ghim's notebooks and that the pages contain Dr. Ghim's handwriting. (SX 2066, ¶ 12).

47. Dr. Wlazlo testifies that he has reviewed exhibits SX 2079 through 2084 and to the best of his knowledge, "Dr. Ghim performed the work recorded therein on or about the dates set forth in such exhibits." (SX 2074, ¶ 50).

48. Dr. Ghim testifies as to various experiments that she performed during the months of October and November 1990 that relate to HPV-1 L1. (SX 2073, ¶¶ 11-18).

49. Dr. Wlazlo testifies that to the best of his knowledge, he observed Dr. Ghim performing the experiments described in Schlegel exhibits SX 2079 through 2084. (*Id.*).

50. Dr. Wlazlo specifically testifies that during the time period of October 1990 to June 1992:

> Dr. Ghim was working on a project to product [sic, produce] a recombinant protein of a papillomavirus. The recombinant protein was to have conformational epitopes of L1 protein as found on intact virions, i.e., the recombinant L1 protein was to reproduce the antigenicity and have the same conformation as L1 protein of intact virions, and which are capable of inducing high titer neutralizing antibodies. The recombinant L1 protein would be capable of being bound by conformational antibodies.

(SX 2074, ¶ 50).

51. Schlegel does not identify where Dr. Ghim's notebooks were contemporaneously signed by a witness.

52. Dr. Ghim and her notebooks tell a consistent and plausible story concerning her alleged work in Dr. Jenson's laboratory.

53. Rose does not challenge Dr. Ghim's allegation that she performed the work identified in her notebooks.

54. Based upon the testimony of Dr. Jenson and Dr. Wlazlo and the consistency between Dr. Ghim's testimony and her notebook notations, we credit Dr. Ghim's testimony and conclude that she performed the work recorded in her notebooks on the dates identified in the notebooks.

e. January 27, 1991 Grant Application

55. Dr. Jenson and Dr. Ghim signed an application for American Podiatric Medical Association's Research Grant Program entitled "Role of antibodies in the treatment of plantar warts." (SX 2086).

56. Dr. Jenson testifies that he and Dr. Ghim prepared the grant application, SX 2086, prior to January 27, 1991. (SX 2066, ¶ 20).

57. Dr. Jenson testifies that the application was read and understood by himself and Dr. Ghim and was signed on or about January 27, 1991. (*Id.*).

58. Dr. Ghim testifies that she signed the grant application, SX 2086, on January 27, 1991. (SX 2070, ¶ 81).

59. The grant application contains a section on experimental design and methods. The following discussion appears under this section:

> In this laboratory, we possess several reagents necessary for this study to be successful: a) Transformed E.coli's containing HPV1-L1 gene (pKK223-H1-L1) and L2 gene (pKK223-H1-L2) expression vectors. They were originally constructed in an attempt to assemble conformational capsid epitopes of HPV1 *in vitro* by attempting to combine the L1 protein with the L2 protein as well as define possible conditions for L1 to fold into different conformations. Our purpose has been the preparation of a vaccine to HPV1, since we observed that only intact BPV1 virion and empty particles purified from infected lesions stimulated the production of type-specific antibodies which neutralized BPV1 infection of C127 cells *in vitro* and xenografts of nu/nu mice *in vivo* (unpublished data).

(SX 2086, pages 14-15).

f. Antibody Binding

60. Dr. Ghim testifies that she conducted testing in October and December, 1989, which demonstrates that antibodies 405D5, 334B6, 339B6 and D54G10 and antiserum #7 bind conformational epitopes of HPV-1 L1 protein. (SX 2072, ¶ 73).

61. As we understand the record, Dr. Ghim tested antibody binding strength using a type of ELISA method. In Dr. Ghim's ELISA method high signal strength represents high levels of antibody concentration whereas low signal strength represents low levels of antibody concentration.

62. According to Dr. Ghim, she conducted ELISA assay testing on purified HPV-1 L1 virions, where the virions were purified by extraction, centrifuged in a CsCl gradient, and dialyzed against phosphate buffered saline ("PBS"). (SX 2072, ¶ 73).

63. Dr. Ghim testifies that the ELISA assays she conducted involved coating samples containing HPV-1 L1 protein, or a disrupted HPV-1 virion[2] onto the wells of an ELISA plate where they were immobilized. The samples were then contacted with an antibody of interest followed by contact with an alkaline phosphatase-conjugated antibody. The ELISA plates were then washed and developed with a phosphatase substrate and the absorbance of the plate wells was then measured. (*Id.* at ¶¶ 25-29 and 79).

I. Pass #7 Antiserum

64. Dr. Ghim testifies that she tested Pass #7 antiserum for conformational binding to HPV-1 L1 on October 13, 1989 and that the results of this testing are reported in her notebook (SX 2080) at page 48 (Bates Stamp Page 451). (SX 2072, ¶¶ 73, 75).

[2]We understand disrupted virions to be denatured, i.e., no longer having conformational epitopes such that monoclonal conformational antibodies will no longer specifically bind the virion.

65. Dr. Ghim testifies that the ELISA assay test results on Bates Stamp Page 451 of her notebook show results in grid form where column 2 represents HPV-1 at a 1:20 dilution and column 3 is HPV-1 at 1:50 dilution where row A represents testing Pass # 7 against intact HPV-1 and row E represents Pass #7 against disrupted HPV-1. (SX 2072, ¶ 75).

66. Dr. Ghim's notebook, SX 2080, Bates Stamp Page 451 contains a grid printout and several handwritten notations. Handwritten notations of interest include:

i) Rows A-D are "intact" virion and rows E-H are "disrupted;"
ii) Column 2 represents "HPV1 (½0)" and column 3 represents "HPV1 (1/50);"
iii) Rows "A & E: Pc #7 (½50);"
iv) The date of testing was "10/13th/89."

(SX 2080, Bates Stamp Page 451).

67. For Pass #7 serum against intact virions, Dr. Ghim's notebook, SX 2080, Bates Stamp Page 451, reports "over" and 1.456 for HPV-1 at 1:20 and 1:50 dilution respectively.

68. For Pass #7 serum against disrupted virions, Dr. Ghim's notebook, SX 2080, Bates Stamp Page 451, reports 0.073 and 0.049 for HPV-1 at 1:20 and 1:50 dilution respectively.

69. Based upon her October 13, 1989 test results, Dr. Ghim testifies that she knew that: 1) "Pass #7 antiserum binds to intact HPV-1 virions and does not bind to disrupted HPV-1 virions;" and 2) the results demonstrate that "Pass #7 antiserum is specific to conformational epitopes of HPV-1 L1 protein." (SX 2072, ¶ 78).

70. Dr. Steinberg, testifying for Schlegel, reviewed Dr. Ghim's notebook SX 2080, Bates Stamp Page 451, and arrives at the same conclusion as that of Dr. Ghim, that Pass #7 antiserum binds conformational epitopes on HPV-1 L1 protein. (SX 2088, ¶¶ 49-53).

71. Dr. Steinberg testifies that Dr. Ghim's ELISA testing of Pass #7 antiserum demonstrates that Pass #7, when diluted, binds detectably only to conformational epitopes on HPV-1 L1. (SX 2126, ¶¶ 5-7).

ii. Antibodies 334B6 and 405D5

As discussed below, there appears to be two distinct and potentially conflicting sets of data in the record concerning Dr. Ghim's December 1, 1989 testing regarding antibodies 334B6 and 405D5. Specifically, both Schlegel exhibits SX 2097 and SX 2080 appear to contain ELISA test data concerning Dr. Ghim's December 1, 1989 testing with monoclonal antibodies 334B6 and 405D5.

72. Dr. Ghim testifies that she tested antibodies 334B6 and 405D5 for conformational binding to HPV-1 L1 on December 1, 1989 and that the results of this testing are reported in her lab notebook (SX 2080) at page 38 (Bates Stamp Page 417). (SX 2072, ¶¶ 79, 81).

73. Dr. Ghim identifies a notebook page "38" (SX 2080, Bates Stamp Page 415) as containing her contemporaneous notes regarding the ELISA testing of antibodies 334B6 and 405D5. (SX 2072, ¶ 81).

74. SX 2080, Bates Stamp Page 415, contains handwritten notations including a date of "December 1st 1989" and two tables labeled "I" and "II" under a heading of "Type of MAB by ELiSA."

75. Dr. Ghim identifies a notebook page, SX 2080, Bates Stamp Page 417, as containing a printout of the data she obtained from her December 1, 1989 ELISA tests with, among other things, antibodies 334B6 and 405D5. (SX 2072, ¶ 81).

76. SX 2080, Bates Stamp Page 417 contains a first table labeled "Plate ID: I" with a date of "1st Dec. 1989" and a second table, underneath the first, labeled "Plate ID: II."

77. Dr. Ghim testifies that the ELISA results for antibody 334B6 are shown in Table II, Rows B through E and columns 3 and 4 on Bates Stamp Pages 415 and 417. (SX 2072, ¶ 81).

78. According to Dr. Ghim, the ELISA data shows that for a 1/100 dilution the 334B6 antibody had values of 0.657 and 0.561 against intact HPV-1 virions and values of -0.20 and -0.016 against disrupted HPV-1 virions. (*Id.*, relying on Bates Stamp Pages 415 and 417, Row B, cols. 3 and 4 and Row D cols. 3 and 4).

79. According to Dr. Ghim, the ELISA data shows that for a 1/500 dilution the 334B6 antibody had value of 0.756 and 0.659 against intact HPV-1 virions and values of -0.23 and -0.026 against disrupted HPV-1 virions. (*Id.*, relying on Bates Stamp Pages 415 and 417, Row C, cols. 3 and 4 and Row E cols. 3 and 4).

80. According to Dr. Ghim, the ELISA data for antibody 405D5 at 1/100 dilution was 0.545 against intact HPV-1 virion and 0.000 against disrupted virion. (SX 2072, ¶ 83, relying on Bates Stamp Pages 415 and 417, Row G, cols. 7 and 8).

81. According to Dr. Ghim, the ELISA data for antibody 405D5 at 1/500 dilution was 0.547 against intact HPV-1 virion and -0.012 against disrupted virion. (SX 2072, ¶ 83, relying on Bates Stamp Pages 415 and 417, Row H, cols. 7 and 8).

82. Based upon her ELISA test results, Dr. Ghim concludes that "monoclonal antibodies 334B6 and 405D5 are specific to conformational epitopes on the surface of intact HPV-1 virions." (SX 2072, ¶ 84).

83. Dr. Steinberg, testifying for Schlegel, reviewed Bates Stamp Pages 415 and 417 of Dr. Ghim's notebook SX 2080, and arrives at the same conclusion as that of Dr. Ghim, that antibodies 334B6 and 405D5 binds conformational epitopes on HPV-1 L1 protein. (SX 2088, ¶¶ 54-58).

84. Rose cross-examined Dr. Steinberg regarding her conclusions that antibodies 334B6 and 405D5 bind conformational epitopes. (SX 2107, e.g., p. 143, line 10 to p. 144, line 1).

85. During cross-examination, Rose identified SX 2097 as containing what appeared to be a compilation of several exhibits including several taken from research notebooks of Dr. Ghim. (SX 2107, p. 138, line 21 to p. 139, line 5).

86. Bates Stamp Page 264 of SX 2097 contains handwritten notations including a date of "December 1st 1989" and two tables labeled "I" and "II" under a heading of "Type of MAB by ELiSA."

87. Bates Stamp Page 264 of SX 2097 appears identical to that of Bates Stamp Page 415 of SX 2080 except that page 415 contains a notation "38" and page 264 contains circles around the Table II identification of the 334B6 and 405D5 antibody testing.

88. Bates Stamp Page 265 of SX 2097 contains the notations "Plate ID: II" and "1st Dec. 1989" and presents data that differs from that of "Plate ID:II" of Bates Stamp Page 417 of SX 2080.

89. Intermixed with the printed data on Bates Stamp Page 265 are notations that appear to be "334B6x," "334B6y" and "405D5" along with various circles surrounding particular blocks of data.

90. Above the data presented in Bates Stamp Page 265 is the notation: "[o]nly two Mabs (334B6 and 405D5) are specific to HPV1. But they recognize it only after denaturation of V. prot."

91. Based upon the record presented, we are uncertain as to whether the ELISA data on Bates Stamp Page 265 or the data on Bates Stamp Page 417 or both correspond to the ELISA Table II explanations appearing on both Bates Stamp Pages 264 and 415.[3]

[3]Dr. Ghim's record keeping procedures and notebooks are, at times, haphazard.

92. During the cross-examination of Dr. Steinberg on January 12, 2005, Dr. Steinberg stated that the data on Bates Stamp Page 265 demonstrated some reactivity between 334B6 and 405D5 with the disrupted HPV-1 L1 protein, but that the reactivity was preferentially with the intact HPV-1 L1. (SX 2107, p. 144, line 20 to p. 145, line 6).

93. During cross-examination, Dr. Steinberg admitted that, if she only had the data presented in Bates Stamp Page 265, there is enough reaction with the disrupted virion that she would have to repeat the experiment to determine whether the 334B6 and 405D5 antibodies bind linear epitopes. (*Id.* at p. 145, line 22 to p. 148, line 2).

iii. Monoclonal Antibodies 339B6, D54G10 and 370D5

94. Dr. Ghim testifies that on December 1, 1989, she tested monoclonal antibodies 339B6, D54G10 and 370D5 in ELISA assays to determine whether these antibodies bind conformational epitopes on HPV-1 virions. (SX 2072, ¶ 85).

95. Dr. Ghim testifies, and Rose's Opposition Brief (Paper No. 78) does not contest, that her ELISA test notes and results are found at Bates Stamp Pages 416 and 420 of SX 2080. (SX 2072, ¶¶ 87-88).

96. Notebook Bates Stamp Page 416 of SX 2080 contains two handwritten tables labeled "III" and "IV" where column 9 of Table III contains notations including "D54G10" in Row B, "370D5" in Row F, and "339-B6" in Row A.

97. Notebook Bates Stamp Page 420 of SX 2080 is a printed table with what appears to be test results and is labeled "Plate ID: III" and has a notation of "1/12," which is consistent with Dr. Ghim's testimony that the test occurred on December 1, 1991. Column 11 contains the highest values in the table, and the values in col. 11, rows B, F, and G are circled.

98. Dr. Ghim testifies that column 11 contains the ELISA absorbance for antibody binding with intact HPV-1, while column 12 contains the ELISA absorbance values for antibody binding with disrupted HPV-1 virions. According to Dr. Ghim, the data shows that:

i. Antibody 339B6 intact HPV-1 = 0.187 and disrupted HPV-1 = -0.017
ii. Antibody D5G10 intact HPV-1 = 0.139 and disrupted HPV-1 = 0.004
iii. Antibody 370D5 intact HPV-1 = 0.142 and disrupted HPV-1 = 0.005

(See, SX 2072, ¶¶ 88-92, and SX 2080, Bates Stamp Pages 416 and 420)

99. Dr. Ghim and Dr. Steinberg conclude that Dr. Ghim's ELISA test results demonstrate that antibodies 339B6, D54G10 and 370B5 bind HPV-1 virions but not disrupted HPV-1 virions and that this distinction demonstrates that these particular antibodies are specific to conformational epitopes on the surface of HPV-1 virions. (SX 2072, ¶ 93; SX 2088, ¶ 66).

iv. Dr. Ghim's October 29, 1991 Retesting of the Binding Properties of 405D5, 334B6, 339B6 and D54G10 and antiserum #7

100. Dr. Ghim testifies that she conducted ELISA testing on October 29, 1991 that verified her previous finding that monoclonal antibodies 405D5, 339B6, D54G10, 334B6 and rabbit antiserum #7 ("Pass #7") bound only to conformational epitopes located on intact HPV-1 virions. (SX 2072, ¶ 94).

101. According to Dr. Ghim, her October 29, 1991 ELISA antibody testing is recorded on Bates Stamp Pages 269, 270 and 272 of SX 2079. (*Id.* at ¶ 97).

102. Each of Bates Stamp Pages 269 and 270 of SX 2079 is dated "October 29, 91" and both contain a handwritten table listing antibodies, dilutions and contain columns having the notations "int," "dis" and "BG."

103. Bates Stamp Pages 269 and 270 indicate that the ELISA testing was run with varying dilutions of the antibody samples. For example, Bates Stamp Page 270 contains a table labeled "Plate I" with the following information taken from row G of the table:

		int	dis	BG	int	dis	BG	int	dis	BG
	1	2	3	4	5	6	7	8	9	10
G		Pass #7 ½50			1/500			1/1000		

(SX 2079, Bates Stamp Page 270).

104. Dr. Ghim testifies that the notations "int," "dis" and "BG" are shorthand for "intact," "disrupted" and "background." (SX 2072, ¶ 103).

105. Beneath the handwritten tables on SX 2079 Bates Stamp Pages 269 and 270 is a tabulation of data.

106. The following information is present on row G of the tabulated data:

	1	2	3	4	5	6	7	8	9	10
G	-0.033	1.501	0.010	0.008	1.090	0.008	0.008	0.630	0.009	0.010

(SX 2079, Bates Stamp Page 270).

107. According to Dr. Ghim, the correct ELISA value for each antibody tested is determined by subtracting the background value from the intact or disrupted value. (SX 2072, ¶ 103).

108. Dr. Ghim testifies that certain October 29, 1991 ELISA test results, taking into account the subtracted background value, appear on Bates Stamp Page 272 and again in Table IV of U.S. Patent Application 08/216,506 (SX 2023, p. 44). (SX 2072, ¶ 104).

109. Dr. Ghim and Dr. Steinberg testify that the October 29, 1991 ELISA results demonstrate that monoclonal antibodies 405D5, 339B6, D54G10, 334B6 and rabbit antiserum #7 (Pass #7) bind only to conformational epitopes located on intact HPV-1 virions whereas monoclonal antibody MAB45 and Pass #3 antiserum bind linear, non-conformational epitopes on HPV-1 virion. (SX 2072, ¶¶ 105-106 and SX 2088, ¶¶ 72-73).

110. Consistent with Dr. Ghim's testimony, Bates Stamp Pages 269 and 270 appear to report the results of Dr. Ghim's October 29, 1991 ELISA assay. While not inconsistent with her testimony, we note that the record copy of Bates Stamp Page 270 of SX 2079 does not identify a specific dilution ratio for 339B6 and instead has only tiny dark spots where the dilution value would be recorded. We do not know whether the record copy in this interference is a poor

photocopy of the original notebook page or whether the original also contains only tiny dark spots.

111. A review of the tabulated, printed data appearing in Dr. Ghim's notebook, as interpreted in light of both the handwritten notes located above the tabulation and Dr. Ghim's testimony, demonstrates that significantly higher ELISA values were reported against the intact HPV-1 virion as opposed to the disrupted HPV-1 virion for monoclonal antibodies 405D5, 339B6, D54G10, 334B6 and diluted rabbit antiserum #7 (Pass #7). In comparison, the ELISA values for the MAB45 monoclonal antibody and Pass #3 were only slightly higher for the intact HPV-1 virion as opposed to the disrupted HPV-1 virion.

v. Rose's Critique of Schlegel's Conformational Antibody Binding Testing

112. Rose's expert, Dr. Martin Josef Sapp, testifies that rabbit antiserum #7, which is also referred to as Pass #7, has not been shown to bind specifically to only conformational epitopes on HPV-1 L1. (Third Declaration of Dr. Sapp, RX 4222, ¶ 6).

113. To support his conclusion regarding Pass #7 binding properties, Dr. Sapp relies upon Dr. Ghim's laboratory notebook's statement that Pass #7 probably pulls down (reacts with) linearized epitopes. (RX 4222, ¶ 8 citing Ghim Notebook, SX 2079, Bates Stamp Page 312: "Pass #7 ↓ probably linearized epitopes").

114. Schlegel's involved '506 patent application states that rabbit #7 antiserum was described in Pass, F. and Maizel, J.V., J. Invest. Dermatol. 60:307-311 (1973). ('506 application, SX 2023, p. 43, lines 14-18).

115. Dr. Sapp testifies that Figure 5 of the Pass article (FX 1161) demonstrates that Pass #7 antiserum "has been shown by Ouchterlony double diffusion assays to react with the denatured major capsid protein of purified virions eluted from SDS polyacrylamide gels." (RX 4222, ¶ 7, citing FX 1161, Fig. 5).

116. Figure 5 in the record copy of FX 1161 depicts a barely distinguishable black and white picture of what is said to be six peripheral wells around a center well with the six peripheral wells having varying degrees of white spots, the presence of which appears to indicate binding of a tested antibody and a disrupted HPV virion.

117. Both Dr. Sapp and Schlegel's expert, Dr. Steinberg, agree that Figure 5 of the Pass article suggests that Pass #7 antiserum reacts with linear epitopes. (RX 4222, ¶ 7; SX 2107, 131:4-132:9 and 140:11-141:15).

118. Dr. Steinberg, testifying for Schlegel, states that:

> Notwithstanding the expected presence of antibodies that bind to linear epitopes, depending upon the relative amounts of antibodies that bind to conformational epitopes and antibodies that bind to linear epitopes, it is possible to dilute a polyclonal antiserum raised against HPV1 virions such that only the conformational antibodies present therein are capable of binding detectably to an HPV1 L1 protein.

(SX 2126, ¶ 4).

119. Dr. Steinberg also testifies that:

> Dr. Ghim's testing demonstrates that Pass #7 antiserum could be diluted in a manner such that Pass #7 only binds detectably to conformational epitopes.

(SX 2126, ¶ 5, citing Dr. Ghim Notebook, SX 2080, Bates Stamp Page 451, and SX 2079, Bates Stamp Page 270).

120. Dr. Sapp testifies that there is no assurance that the reactivity of Schlegel's Pass #7 antiserum was due to binding HPV-1 L1 protein as opposed to a contaminant. (RX 4222, ¶ 9).

121. Although Dr. Sapp testifies that Schlegel's ELISAs do not exclude the possibility that the reported reactivity is due to Pass # 7 binding a contaminant, which was destroyed upon denaturation, Dr. Sapp does not point to any indications that such a contaminant was present, nor does he estimate the likelihood of the proposed "possibility."

122. Dr. Steinberg, testifying for Schlegel, states that Dr. Sapp's allegations regarding contamination are speculative and that there is no evidence suggesting that the HPV1 virions contain contaminating material binding Pass #7. (SX 2126, ¶¶ 8-10).

123. In this regard, we credit the testimony of Dr. Steinberg and conclude that Dr. Sapp's "contaminant" argument is speculative as Dr. Sapp fails to identify positive indications beyond mere ever present possibilities, that a contaminant, which binds with Pass #7 but not after denaturation, was present in Dr. Ghim's Pass #7 testing.

124. Dr. Sapp testifies that Pass #7 has not been shown to be neutralizing and that the exact HPV serotype of virions used to generate Pass #7 antiserum was never determined. (*Id* at ¶ 10). Dr. Sapp takes the position that had Pass #7 been shown to be neutralizing it would constitute

proof "that this antiserum did bind to conformationally intact epitopes exposed on the surface of HPV-1 virions. (*Id.*).

125. Dr. Sapp testifies that monoclonal antibodies 405D5, 339B6, D54G10, 334B6 and 370D5 have not been characterized with respect to the specific protein that they bind and that Schlegel has failed to demonstrate that these antibodies are neutralizing. (*Id.* at ¶¶ 12-13). Dr. Sapp does not state that a demonstration of neutralization or protein characterization is necessary to demonstrate that Pass #7 antiserum binds conformational epitopes.

126. Dr. Sapp testifies that Schlegel has failed to provide sufficient information regarding the quality of Schlegel's preparations and thus one cannot exclude the possibility that Schlegel's ELISA assays with monoclonal antibodies 405D5, 339B6, D54G10, 334B6 and 370D5 contained a contaminant that binds the antibodies, but is destroyed upon denaturation. (*Id.* at ¶ 12).

127. Dr. Sapp does not point to any indications that such a contaminant was present in Schlegel's ELISA assays with monoclonal antibodies 405D5, 339B6, D54G10, 334B6 and 370D5, nor does he estimate the likelihood of the proposed "possibility."

128. We conclude that Dr. Sapp's "contaminant" argument is speculative as Dr. Sapp fails to convincingly identify a reasonable basis for believing that a contaminant, which binds with Schlegel's monoclonal antibodies but not after denaturation, may have been present in Dr. Ghim's ELISA testing.

vi. Conclusions Regarding Schlegel Antibody Conformational Binding

129. We find that the preponderance of the evidence, including Dr. Ghim's December 1, 1989 and October 29, 1991 ELISA testing, indicates that monoclonal antibodies 339B6, D54G10 and 370D5 specifically bind conformational epitopes on HPV-1 virons.

130. The parties have identified two distinct sets of data for Dr. Ghim's December 1, 1989 ELISA testing of monoclonal antibodies 334B6 and 405D5 and the data sets yield different interpretations. Given the confusion regarding the nature of the December 1, 1989 data, we find that the preponderance of Schlegel's evidence does not establish that monoclonal antibodies 334B6 and 405D5 specifically bind conformational epitopes as opposed to linear epitopes on HPV-1 virion.

131. The evidence of record demonstrates that Pass #7 antiserum binds to both conformational and linear epitopes with a significant preference for conformational epitopes.

132. The record demonstrates further that dilution of the Pass #7 antiserum can result in an ELISA absorbance from conformational binding only.

133. We credit the testimony of Dr. Steinberg, which has been subjected to cross-examination, and conclude that the ordinary worker aware of the Pass article and Dr. Ghim's December 1, 1989 and October 29, 1991 ELISA testing would have possessed a reasonable expectation that a demonstration of binding between diluted Pass #7 antiserum and HPV-1 L1 is consistent with conformational, as opposed to linear, epitope binding.

134. However, one of ordinary skill in the art, aware that diluted Pass #7 bound a particular recombinant HPV-1 L1, would have required additional testing or information before concluding that the recombinant HPV-1 L1 possessed conformational epitopes. This issue is discussed further with respect to Schlegel's actual reduction to practice.

135. Dr. Ghim's December 3, 1991 ELISA testing on isolated recombinant HPV-1 L1 with Pass #7 antiserum, where the Pass #7 bound the recombinant HPV-1 L1, fails to establish that Pass #7 bound recombinant HPV-1 L1 conformational epitopes.

g. Placing HPV-1 L1 DNA into a Cell to Express HPV-1 L1 Protein

136. Dr. Ghim testifies that on September 25, 1991 she obtained DNA encoding the L1 protein of HPV-1. (SX 2072, ¶ 34).

137. Dr. Ghim testifies that on September 25, 1991 she used PCR primers S1 and S2 to amplify the HPV-1 L1 gene and then verified the presence of the HPV-1 L1 gene in the PCR product. (*Id.* at ¶ 35).

138. Dr. Ghim's testimony is consistent with the notations in her notebook entry dated September 25, 1991 , e.g., "Primers for the cloning of HPV_1 L1 gene in pSVL expression vector. (SX 2079, Bates Stamp Pages 237-239)

139. Dr. Ghim testifies that she ran the PCR product, a control protein and a 1 kb ladder on a gel, which separates the PCR product on the basis of molecular weight. Dr. Ghim testifies that the gel is shown in her notebook (SX 2079) at Bates Stamp Page 238.

140. Bates Stamp Page 238 (SX 2079) contains black strip in the lower left hand corner with a handwritten notation "1.6kb →" at about the midpoint of the black strip.

141. Dr. Ghim testifies that the "1.6kb" notation on Bates Stamp Page 238 (SX 2079) represents the size of the PCR product and that the 1.6kb size is the correct size for HPV-1 L1. (SX 2072, ¶ 40).

142. Dr. Steinberg testifies that Dr. Ghim's "1.6" notation "shows the location of the band on the gel which corresponds to the 1.6kb HPV-1 L1 genomic DNA." (SX 2088, ¶ 25).

143. Dr. Ghim testifies that she conducted a second PCR reaction that provided an HPV-1 L1 gene that was later inserted into a pSVL vector. (SX 2072, ¶ 41). This testimony is consistent with Dr. Ghim's notebook page entries on Bates Stamp Page 239 (SX 2079), where she identified the reactants and amounts for the PCR reaction amplifying the L1 and L2 gene.

144. Dr. Ghim testifies that from the end of September to October 15, 1991, she worked on inserting the HPV-1 L1 DNA into the pSVL vector. (SX 2072, ¶ 42). Dr. Ghim's notebooks appear consistent with Dr. Ghim's testimony as they describe the ligation of L1 and L2, precipitation and transformation. (See, e.g., SX 2079, Bates Stamp Page 240).

145. Dr. Ghim testifies that she conducted several DNA "minipreps" of E. coli cells transfected with pSVL vector including HPV-1 L1 DNA to verify the insertion of the HPV-1 L1 DNA into a construct, also known as plasmid vector pSVL. (SX 2072, ¶ 44). Dr. Ghim's testimony is consistent with the notations in her notebook that describe minipreps of L1 DNA

and L2 DNA with L1 being present in vectors 1, 2, 3, 7 and 9 and L2 present in vectors 3, 4, 9 and 11. (See, e.g., SX 2079, Bates Stamp Page 240).

146. Dr. Ghim testifies that she conducted "maxipreps" and selected the 1-9 vector, noting that the L1 1-1 and 1-3 vectors appeared to have mutations. (SX 2072, ¶ 44). This testimony is consistent with the notations contained in Dr. Ghim's notebook (SX 2079), for example "verification of insertion and mutation" with restriction enzyme, "study on #" with the numbers 1, 7 and 9 circled for L1, and that L1 vectors 1-1 and 1-3 "seem to have mutation." (SX 2079, Bates Stamp Pages 249-250).

147. Dr. Ghim testifies that she transfected cos cells with the 1-9 pSVL vector that contained HPV-1 L1 DNA. Transfection was accomplished by precipation, glycerol shock, incubation, washing of the cells and the subsequent addition of a new medium. (SX 2072, ¶¶ 58-63). Dr. Ghim's notebook, while not the most legible, contains notations referring to L1 (1-9) and L2 (1-9), "trypsination," "preparation of DNA," and a listing of steps under the heading of "Transfection," where the steps include what appears to be a $CaCl_2$ precipitation, a glycerol shock, incubation, washing with PBS, and the addition of a new medium. (SX 2079, Bates Stamp Pages 252 and 255).

148. We understand that Schlegel transfected the cos cells to produce HPV-1 L1 protein.

2. Schlegel's Alleged Reduction to Practice Dates

a. First Reduction: October 23, 1991

149. Dr. Ghim testifies that on October 23, 1991, she performed an immunofluorescence assay with the 1-9 HPV-1 L1/pSVL construct and antibodies, the antibodies including rabbit antiserum #7, and monoclonal antibodies 405D5, 339B6, D54G10, 334B6 and 370D5. (SX 2072, ¶¶ 64-66).

150. According to Dr. Ghim, the immunofluorescence test involved trypsinizing the transfected cos cells, washing once with PBS and then placing one drop of cells on a well. (SX 2072, ¶ 70).

151. Dr. Ghim testifies that a positive result, binding, was indicated for the 1-9 HPV-1 L1/pSVL construct with monoclonal antibodies 405D5, 339B6, D54G10, 334B6 and 370D5 and rabbit antiserum #7, and that negative results, no detectable binding, was found when these antibodies were tested against cos cells transfected with a pSVL control vector. (SX 2072, ¶ 72).

152. Dr. Ghim testifies that her notes regarding her October 23, 1991 immunofluorescence test are found at notebook SX 2079, Bates Stamp Page 260. (SX 2072, ¶¶ 70, 72).

153. Dr. Ghim's notations on notebook SX 2079, Bates Stamp Page 260, are consistent with her testimony. Specifically, the notebook page bears a notation "<Oct. 23rd 91>" as well as notations identifying "trypsinate transfected cells," washing once with PBS and "put one drop on the side which has the wells." The notebook page also includes a table listing antibodies in rows and four separate columns labeled L1, L2, L1+L2 and "control (pSLV)." The table on notebook

page 260 identifies the antibodies 405D5, 339B6, D54G10, 334B6 and 370D5 and rabbit antiserum #7 as having a "+" binding with L1 and a "-" binding with the control pSVL.

154. Dr. Ghim testifies that:

> These results show that the cos cells that were transfected with the 1-9 HPV-1 L1/pSVL construct express an HPV-1 L1 protein which is recognized by antibodies and an antiserum which bind to conformational epitopes of HPV-1 L1 virions, and thus the HPV-1 L1 protein expressed by the cos cells transfected with the 1-9 HPV-1 L1/pSVL construct has conformational epitopes.

(SX 2072, ¶ 72).

155. According to Dr. Sapp, Schlegel does not identify any separation of the recombinant HPV-1 L1 from the cos cell material for the October 23, 1991 immunofluorescence assay. (RX 4222, ¶ 15).

b. Second Reduction: November 3, 1991

156. Dr. Ghim testifies that she conducted a second immunofluorescence test on the 1-9 HPV-1 L1/pSVL construct on November 3, 1991. (SX 2072, ¶ 108).

157. The November 3, 1991 immunofluorescence test was conducted on the 1-9 construct and several antibodies, including 405D5 and Pass #7 antiserum. Dr. Ghim testifies that the 405D5 antibody and the Pass #7 antiserum bound to the product expressed by the HPV-1 L1/pSVL transfected cos cells but not to the control pSVL. (*Id.* at ¶¶ 110, 115-16).

158. Dr. Ghim testifies that the immunofluorescence assay and results are described on Bates Stamp Page 278 of her notebook (SX 2079). (*Id.* at115).

159. Bates Stamp Page 278 of notebook SX 2079 contains notations that are consistent with Dr. Ghim's testimony. For example, the page contains a date of "Nov. 3rd 91" and identifies results such as "pass #7 + on L1 and L1 + L2, but - on L2 and C-" and "405D5 + on L1 and L1 +L2, but - on L2 and C-."

160. Schlegel does not identify any separation of the recombinant HPV-1 L1 from the cos cell material for the October 23, 1991 immunofluorescence assay. (RX 4222, ¶¶ 15 and 18).

c. Third Reduction: December 3, 1991

161. Dr. Ghim testifies that beginning in the last week of November 1991, she separated HPV-1 L1 protein from a lysate of cos cells that were transfected with a pSVL vector. (SX 2072, ¶ 118). Consistent with her testimony, Dr. Ghim's notebook (SX 2079), Bates Stamp Page 300 is captioned "Purification of Capsid prot. I," and contains a notation "from last week of November to 1st week of D."[4]

162. Dr. Ghim states that she transfected cos cells with the 1-9 HPV-1 L1/pSVL construct vector and with the 2-9 HPV-1 L2/pSVL construct vector. (*Id.* at ¶ 119).

163. Dr. Ghim testifies that she labeled the transfected cos cells with ^{35} S-methionine, lysed the cells and then centrifuged the lysate. (*Id.* at ¶ 120).

[4]Many of the handwritten notations in the record copy of Bates Stamp Page 301 (SX 2079) are difficult to read or illegible. For example, after the notation "(1) labeling:" there is a notation that we have not been able to decipher.

164. Dr. Ghim testifies that she collected the supernatant from the centrifugation in the Sorvall rotor, described above, and centrifuged it to pellets in a Beckman 45 ti rotor for 2 hours at 36,000 rpm. Dr. Ghim testifies that the resulting pellet fraction included proteins, including HPV-1 L1 protein. (*Id.* at ¶ 131).

165. Dr. Ghim's notebook, Bates Stamp Page 301, contains notations that are consistent with her testimony including "(1) labeling:," "(2) lysis:," "25' (NP40 sol'n)," "(3) (c): @ 10,000 rpm sorvall" and "(4) pelletizing: take supernatant @ 2 hrs (45Ti, 36k rpm)."

166. We cannot confirm every detail of Dr. Ghim's testimony regarding her December 1, 1991 notebook. For example, she states that her notebook contains a notation "labeled w/ ^{35} S-methionine" but the record copy of Bates Stamp Page 301 is not legible on this point. Rose's opposition, however, does not contest Dr. Ghim's testimony on this point. However, Dr. Ghim's notebook (SX 2079), Bates Stamp Pages 301 and 302 contain printouts from what appears to be a test measuring "S-35" isotope from samples of the centrifuged pellet material and supernatant.

167. Dr. Ghim testifies that she suspended the pellet material she obtained in CsCl solution and conducted another centrifugation where she obtained nine fractions from the pellet fraction, which are indicated as "culot" on Bates Stamp Page 301 of her notebook (SX 2079). (SX 2072, ¶ 132). Dr. Ghim's notebook (SX 2079), Bates Stamp Page 301, contains a printout of what appears to be a radioactivity test for S-35 isotope on nine samples.

168. Dr. Ghim testifies that fractions 3 through 7 of the pellet had sufficiently high level of 35S-label, indicative of newly synthesized protein content, and subjected them to electron microscopy (IEM). (SX 2072, ¶ 133).

169. Dr. Ghim's notebook contains notations that are consistent with her IEM testimony, e.g., "IEM," "20 µl 1/ 200 pass # 7 + 10 µl sample 5' incubation," "staining" and "observation." (SX 2079, Bates Stamp Page 301).

170. Dr. Ghim testifies that she conducted an ELISA assay on each of the nine pellet fractions, as well as eight supernatant fractions, using Pass #7 antiserum. (SX 2072, ¶ 134). According to Dr. Ghim, she conducted the ELISA assay using 50 µl of each fraction obtained from the pellet at a 1/10 dilution in PBS and ½ dilution in PBS for fractions obtained from the supernatant. (*Id.* at ¶ 137). Dr. Ghim's testimony is consistent with her notebook (SX 2079), which contains the notations "ELISA: 1/10 for culot fraction in PBS 5/45 ½ for supernatant fraction 25/25." (SX 2079, Bates Stamp Page 302).

171. Dr. Ghim testifies that her December 3, 1991 ELISA assay "used the Pass #7 antiserum at a dilution of 1/ 200." (SX 2072, ¶ 138).

172. Dr. Ghim testifies that her ELISA testing results are presented on Bates Stamp Page 303 of her notebook (SX 2079). (SX 2072, ¶ 139). According to Dr. Ghim, and as written in her notebook, (1) column 2 of the printout on Bates Stamp Page 303 represents the first eight culot pellet fractions, (2) column 1 row D represents the ninth culot pellet fraction and (3) column 3 represents the eight supernatant fractions. (*Id.*). Dr. Ghim testifies that the left grid shows the

ELISA results after 10 minutes and the right grid after 30 minutes. (*Id.*). The left and right grids on Bates Stamp Page 303 are marked 10' and 30' respectively.

173. The right grid of Bates Stamp Page 303 at column 2, row G reports identifies the pellet fraction as having an ELISA value of 0.101. (SX 2079). According to Dr. Ghim:

> This result is above the background value and shows that fraction 7 from the pellet materials contained HPV-1 L1 protein having conformational epitopes, which was recognized by the Pass # 7 antiserum. This result therefore shows that I had isolated HPV-1 L1 protein recognized by a conformationally dependent HPV-1 antibody from cos cells transfected with the HPV-1 L1/pSVL construct, determining thus that HPV-1 L1 protein expressed in such cos cells had conformational epitopes.

(SX 2072, ¶ 141).

174. Dr. Steinberg, testifying for Schlegel, states that an accepted practice in ELISA assays is that if an ELISA value is more than two standard deviations above the background value, then the ELISA value is a positive result. (SX 2088, ¶ 95).

175. Dr. Steinberg testifies that her evaluation of Dr. Ghim's December 3, 1991 ELISA values shown in the right grid of Bates Stamp Page 303 led her to conclude that the value of 0.101 shown in Row G, column 2 was more than two standard deviations above the background value and she concludes that this sample tested positive for HPV-1 L1 protein. (SX 2088, ¶ 96). Dr. Steinberg further testifies that testing demonstrates that the HPV-1 L1 protein possessed conformational epitopes present on an L1 protein of an intact HPV-1 virion. (*Id.* at ¶ 97).

176. Dr. Jenson testifies that:

> On or about December 3, 1991, I knew that Dr. Ghim (1) had expressed protein in cos cells that had been transfected with DNA encoding the L1 protein of HPV-1; (2) had isolated the protein expression product from the cells in the form of separate protein fractions by use of cesium chloride gradient centrifugation; and (3) had demonstrated that expressed protein was an L1 protein of HPV-1 that had conformational epitopes of the L1 protein that is part of intact HPV-1 virions by obtaining positive results in an ELISA assay that used an antiserum that was known to bind to conformational epitopes of L1 protein present in an intact HPV-1 virion.

(SX 2066, ¶ 25).

177. Dr. Sapp, testifying for Rose, notes that Dr. Ghim's December 3, 1991 ELISA test "used Pass #7 antiserum" and represents "the first time that the recombinant L1 protein prepared by Schlegel was extracted from cos cells." (RX 4222, ¶¶ 19-20).

178. Dr. Sapp contends that the ELISA value of 0.101 was only "slightly above the background level" and that "it is unclear if this is a significant observation." (*Id.* at ¶ 20).

d. Fourth Reduction: March 16, 1992

179. Dr. Ghim testifies that on March 15 and 16, 1992, she conducted an immunoprecipitation assay on the expression product of cos cells transfected with the 1-9 vector, which contained the HPV-1 L1/pSVL construct. (SX 2072, ¶ 152).

180. Dr. Ghim testifies that she lysed transfected 1-9 cos cells, centrifuged the supernatant of the cell lysate, and reacted the recovered protein with monoclonal antibodies 336B6, D54G10, and 405D5, and Pass #7 antiserum. (*Id.* at ¶ 154).

181. According to Dr. Ghim's testimony, the March 15 and 16, 1992 immunoprecipitation assay demonstrates that monoclonal antibodies 336B6, D54G10 and 405D5 as well as the Pass #7 antiserum bound to HPV-1 L1 protein that had been expressed by the cos cells transfected with the HPV-1 L1/pSVL construct. (*Id.* at ¶ 155).

182. Dr. Ghim testifies that the results from her March 15 and 16, 1992 immunoprecipitation assay are shown on Bates Stamp Pages 330 and 331 of her notebook (SX 2079). (SX 2072, ¶ 157).

183. Dr. Ghim testifies that she reacted the cos cell lysate with the following: (1) 9 µl normal rabbit serum (NRS); (2) 9 µl Pass # 3 antiserum; (3) 9 µl Pass #7 antiserum; (4) 9 µl normal mouse serum (NMS); (5) 150 µl monoclonal antibody 45; (6) 4.5 µl monoclonal antibody 336B6; (7) 4.5 µl 339B6; (8) 150 µl monoclonal antibody D54G10; (9) 4.5 µl monoclonal antibody 405D5. (SX 2072, ¶ 158). Dr. Ghim's notebook (SX 2079), Bates Stamp Page 330, has a handwritten date of "March 15, 92" and contains notations that are consistent with Dr. Ghim's testimony with the exception that normal mouse serum (NMS) is listed as 4.5 as opposed to 9 µl.

184. Dr. Ghim testifies that she ran an SDS-polyacrylamide gel to separate all the proteins bound to the Sepharose-Protein A beads resulting from the immunoprecipitation reaction on March 16, 1992. Dr. Ghim states that a photo obtained from this assay appears in her notebook (SX 2079) at Bates Stamp Page 331, and is also shown at Figure 3 of Schlegel's involved application (SX 2023) and again as Figure 3 of Ghim et al. (SX 2087). (SX 2072, ¶ 159).

185. Dr. Ghim testifies that the immunoprecipitation gel shows molecular weight bands corresponding to HPV-1 L1 protein were recognized by monoclonal antibodies 334B6, 339B6, D54G10 and 405D5 as well as Pass # 7 antiserum. (*Id.*).

186. Bates Stamp Page 331 of Dr. Ghim's notebook (SX 2079) is illegible as it is nearly featureless black. We will not attempt to guess at what is written on this page.

187. Figure 3 of Schlegel's involved application contains an immunoblot and shows binding at a point that is marked "L1 protein," a point between the 43 and 68 kd markers, for Pass # 3, Pass #7, 336B6, 339B6, D54G10 and 405D5. (SX 2023, Figure 3).

188. Dr. Sapp, Rose's expert, testifies that:

> This [Schlegel's March 16, 1992] immunoprecipitation assay followed by SDS-PAGE and autoradiography shows for the first time the presence of a 55 kDa L1 protein that can be extracted in a way that would allow the 405D5, D54G10, and 334B6 monoclonal antibodies and the Pass # 7 antiserum to bind and immunoprecipitate the recombinant L1 protein.

(RX 4222, ¶ 22).

e. Fifth Reduction: March 18, 1992

189. Dr. Ghim testifies that on March 18, 1992 she conducted an immunofluorescence assay to confirm the results of her previous immunofluorescence assays. (SX 2072, ¶ 160).

190. According to Dr. Ghim, cos cells transfected with the 1-9 vector and pSVL as a control were reacted with Pass #7 antiserum. Dr. Ghim states that the 1-9 vector tested positive with Pass #7 and the pSVL was negative. (*Id.* at ¶ 166).

191. Dr. Ghim testifies that her March 18, 1992 immunofluorescence assay is reported on Bates Stamp Page 822 of her notebook (SX 2081). (SX 2072, ¶ 165).

192. Bates Stamp Page 822 contains a handwritten date of "March 18 92" and has notations including "transfected," cos with "HPV_1 L_1/pSVL," cos with "pSVL," cos with BPV_1 L_1/pSVL #88" as well as a table, which under the heading "R α int. HPV_1 # Pass 7" reports "+++" for HPV_1 L_1/pSVL #1-9 and "-" for BPV_1 L_1/pSVL #88" and "pSVL."

193. Dr. Ghim does not state that the March 18, 1992 HPV-1 L1 material was separated from the cos cell material. (RX 4222, ¶¶ 15, 23).

3. Schlegel's Diligence

194. Dr. Ghim testifies that she worked continuously from October 1990 to June 1992 on a project for producing recombinant HPV L1 protein having conformational epitopes of an L1 protein that is part of an intact papillomavirus virion. (SX 2073, ¶ 3).

195. Rose's Opposition Brief on the Issue of Priority (Paper No. 78) does not comment upon Schlegel's alleged diligence towards a reduction to practice between the dates of October 23, 1991 (Schlegel's First Alleged Reduction to Practice) and March 18, 1992 (Schlegel's Fifth Alleged Reduction to Practice).

196. During oral argument counsel for Rose confirmed that Rose does not contest Schlegel's diligence between the dates of October 23, 1991 and March 16, 1992. Specifically, the transcript reads as follows:

Judge Tierney: Speaking of diligence, are you contesting that they were - - are you alleging that they [Schlegel] were not diligent between October 23, 1991 and March 16, 1992?

Mr. Goldman: I don't - - well, I guess it doesn't matter, does it? I mean, from my perspective, we had a diligence gap in May, 20-day diligence gap during that period. So that's right between their filing date and that period. So there's a gap there, if nothing else.

Judge Tierney: But do you have allegations that they [Schlegel] were not diligent between October 23, 1991 and March 16, 1992?

Mr. Goldman: I don't think we do, no.

(Transcript of June 30, 2005 Oral Hearing, Paper No. 98, p. 84, line 13 to p. 85, line 4).

197. Dr. Ghim provides specific testimony describing her work in the laboratory towards an actual reduction to practice for at least the following dates:

1991

October:	23, 25, 29
November:	3, 10, 15, 17, 19, 21 last week November
December:	1-3, 9, 12, 20, 28, 29

1992

January:	2, 5, 7, 8, 9, 10, 12, 13, 14-19, 23, 24, 25, 26, 28, 31
February:	First and second weeks, 14-25, 26, 27
March:	1, 2, 3, 5, 6, 8, 9, 14, 15 and 18

(Fourth Declaration of Dr. Ghim, SX 2073, ¶¶ 120-191).

198. Dr. Ghim testifies that her activities towards a reduction to practice was recorded in her notebooks, in particular, notebooks SX 2079 and SX 2081. (SX 2073, ¶¶ 8-10, 121). Nothing inconsistent with Dr. Ghim's diligence testimony (SX 2073) was found during our review of the specific notebook pages cited by Dr. Ghim.

199. Based upon the record presented, we find that Schlegel has met its burden of proof to establish that it was reasonably diligent from the date of its conception, no earlier than December 3, 1991 to the date of its actual reduction to practice on March 16, 1992, in its efforts to reduce to practice an embodiment falling within the scope of the count.

IV. Opinion

An interference is a procedure to determine who among competing parties was the first to invent a commonly claimed invention. 35 U.S.C. §§ 102(g) and 135(a). The first step in the process is interpreting the Count that defines the interfering subject matter. The second step is establishing priority with respect to the Count.

A. Count Construction

Interference counts are given their broadest reasonable possible interpretation. *Genentech Inc. v. Chiron Corp.*, 112 F.3d 495, 500, 42 USPQ2d 1608, 1612 (Fed. Cir. 1997); *Davis v. Loesch*, 998 F.2d 963, 968, 27 USPQ2d 1440, 1444 (Fed. Cir. 1993). In construing claims that define a count, there is a heavy presumption in favor of the ordinary meaning of claim language. Specifically, a claim term should be given its ordinary meaning as it is understood in the art subject to a special, different meaning or definition provided by the specification. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316-1317, 75 USPQ2d 1321, 1329 (Fed. Cir. 2005) (en banc),

ACTV, Inc. v. Walt Disney Co., 346 F3d 1082, 1091, 68 USPQ2d 1516, 1523 (Fed. Cir. 2003); *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366, 62 USPQ2d 1658, 1662-63 (Fed. Cir. 2002). Claims that provide alternative definitions of the Count are read in light of the specification from which they originate. 37 C.F.R. § 41.200.

Count 1 is the sole count in the '772 interference and includes Rose claims 42, 43, 44, 56, 65 and 71 and Schlegel claims 1, 12, 19, 50, 53, 55 and 64. Schlegel takes the position that it has demonstrated conception, diligence and reduction to practice of an embodiment falling within the scope of the count, and in particular, the portion of the count that includes Schlegel claims 1 and 64. (Schlegel Principal Brief on the Issue of Priority, Paper No. 74, p. 11). Indeed, Schlegel contends that a conception and reduction to practice of Schlegel claim 1 is a conception and reduction to practice of Schlegel claim 64 and vice versa. (*Id.*). Because Schlegel's arguments for priority most clearly conform to Schlegel claim 64, we focus our attention on that claim. Schlegel claim 64 reads as follows:

> 64. **[1]** An isolated **[2]** recombinantly produced **[3]** human papillomavirus (PV) L1 protein, comprising a protein which **[4]** specifically binds to conformational antibodies which react with an L1 protein expressed on the surface of an intact HPV virion.

(Schlegel Principal Brief on the Issue of Priority, Paper No. 74, pages 4-5, Appendix 1, Bold numbers added).

Schlegel claim 64 contains at least four distinct limitations. These limitations and their construction are provided below. Before discussing these limitations we note that the parties' briefs fail to explicitly identify a construction for any of these limitations.

1. Isolated

The parties have not directed our attention to any disclosure in Schlegel's involved '506 specification that explicitly defines the term "isolated." Further, our review of Schlegel's specification failed to reveal a specific definition or any indication that the term has been provided a specialized meaning by Schlegel or by the art. Accordingly, we begin with the presumption that Schlegel has used the term "isolated" consistent with its ordinary and customary meaning. *Brookhill-Wilk 1, LLC, v. Intuitive Surgical, Inc.*, 334 F.3d 1294, 1298, 67 USPQ2d 1132, 1136 (Fed. Cir. 2003) ("The written description must be examined in every case, because it is relevant not only to aid in the claim construction analysis, but also to determine if the presumption of ordinary and customary meaning is rebutted.").

The parties' briefs fail to identify expert testimony that provides a definitive, specialized meaning the term "isolated" may have in the relevant arts. *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1325, 63 USPQ2d 1374, 1380 (Fed. Cir. 2002) ("[T]he ordinary meaning must be determined from the standpoint of a person of ordinary skill in the relevant art.") Accordingly, the ordinary and customary meaning of everyday use is appropriate. A typical definition of "isolate" is "to separate from a group or whole and set apart."[5]

According to Schlegel, the HPV L1 protein is formed in "a host cell to enable the expression of the L1 protein by that cell." (SX 2023, p. 11, lines 1-3). Thus, Schlegel describes the formation of its HPV L1 in a host cell and requires that its HPV L1 be "isolated." Based upon the limited record presented, we construe the term "isolated" as it appears in Schlegel claim 64 as requiring that the HPV L1 protein be separated from the cellular host cell material from which it was formed.

[5] THE AMERICAN HERITAGE DICTIONARY 680 (2d College Ed., 1976)

2. Recombinantly Produced

As with the term "isolated," the parties do not explicitly provide a definition for the term "recombinantly produced." In particular, the parties do not attempt to define the term with reference to Schelgel's specification or testimony from a person of ordinary skill. Accordingly, we provide the term "recombinantly produced" with its ordinary and customary meaning, which, as applied to a protein, generally means that the gene has been inserted into a foreign nucleic acid, transcribed and translated to yield the protein.

3. HPV L1 protein

Schlegel claim 64 is directed to an HPV L1 protein "comprising a protein which specifically binds to conformational antibodies which react with an L1 protein expressed on the surface of an intact HPV virion." Giving Schlegel claim 64 its broadest reasonable interpretation, we conclude that claim 64 requires a protein that is recognized by one of ordinary skill in the art as a recombinant HPV L1 protein having the stated binding properties of specifically binding to conformational antibodies that react with an L1 protein expressed on the surface of an intact HPV virion. This construction of Schlegel claim 64 does not exclude "mutant" HPV L1, nor is Schlegel claim 64 expressly limited to a recombinantly produced protein having the "wild type" sequence.

4. Specifically Binds to Conformational Antibodies, Which React with an L1 Protein Expressed on the Surface of an Intact HPV Virion

As with the other terms used in Schlegel claim 64, the parties fail to specifically define the phrase "specifically binds to conformational antibodies, which react with an L1 protein expressed on the surface of an intact HPV virion." At most, Schlegel argues that its claim 64 requires certain characteristics, in particular, that the recombinant L1 protein specifically binds to

antibodies that recognize a conformational epitope. (Schlegel Principal Brief on Priority, Paper No. 74, p. 10). As the parties have failed to identify an art recognized specific definition for this phrase, we presume that the parties do not dispute that Schlegel used this phrase consistent with its customary and ordinary meaning. We hold that the customary meaning of the phrase "specifically binds to conformational antibodies, which react with an L1 protein expressed on the surface of an intact HPV virion," requires: 1) binding at a level above background levels; and 2) binds an antibody that binds to an L1 conformational epitope on the surface of an intact HPV virion.

Schlegel argues that a conception and/or reduction to practice of Schlegel claim 64 is a conception and/or reduction to practice of Schlegel claim 1. (*Id.* at 11). Specifically, Schlegel states that "the fact that a recombinant human papillomavirus L1 protein binds to conformational antibodies that bind to L1 protein on intact virions demonstrates that the recombinant protein has the antigenic properties and conformation of claim 1." (*Id.*). Schlegel relies upon the testimony of its expert, Dr. Steinberg, to support this allegation. (*Id.* citing SX 2076, ¶ 5). Specifically, Dr. Steinberg testifies as follows:

> Dr. Ghim produced a recombinant L1 protein of HPV-1 that specifically binds to conformational antibodies which reacts [sic] with L1 protein expressed on the surface of intact HPV-1 virions. As a result of such binding such recombinant L1 protein and the L1 protein on intact HPV-1 virions have common conformational epitopes, whereby such recombinant HPV-1 L1 protein reproduces the antigenicity and exhibits the same conformation as an L1 major capsid protein expressed on the surface of intact human HPV1 virions.

(SX 2076, ¶ 5).

Schlegel claim 1 requires that the recombinant protein reproduces the antigenicity and that it exhibit the same conformation as a L1 protein on the surface of an intact human papillomavirus. It is not apparent how the demonstration that one or a small number of conformational antibodies that bind specifically to a native virion demonstrates that every

antigenic feature of the native protein has been reproduced. In any event, because we conclude that Schlegel has proved conception, diligence and an actual reduction to practice for an embodiment within the scope of the count, Schlegel claim 64, we need not decide whether or not Schlegel has proved conception or reduction to practice of Schlegel claim 1.

B. Conception

Conception is the formation, in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is thereafter to be applied in practice. *Cooper v. Goldfarb*, 154 F.3d 1321, 1327, 47 USPQ2d 1896, 1901 (Fed. Cir. 1998). The Federal Circuit has indicated that one way to distinguish a "bare hope" from a "complete conception" is to focus "on whether the inventors had a reasonable expectation that they would produce the claimed invention." *Hitzeman v. Rutter*, 243 F.3d 1345, 1358, 58 USPQ2d 1161, 1170 (Fed. Cir. 2001).

Because conception is a mental act, an inventor's testimony, standing alone, is insufficient -- some form of corroboration must be shown. *Price v. Symsek*, 988 F.2d 1187, 1194, 26 USPQ2d 1031, 1036 (Fed. Cir. 1993). We apply a "rule of reason" analysis to determine whether the inventor's prior conception testimony has been corroborated.

1. October 1990

Dr. Schlegel and Dr. Jenson testify that they had discussions, prior to October 1990, regarding working together to develop one or more L1 protein papillomavirus products that could be used as a diagnostic and/or vaccine for papillomavirus. (Dr. Jenson Declaration, SX 2066, ¶ 2, Dr. Schlegel Declaration, SX 2068, ¶ 4). Both Dr. Jenson and Dr. Schlegel testify that they decided that the work would be performed in Dr. Jenson's laboratory. (SX 2066, ¶ 5, SX 2068, ¶ 6). Further, Dr. Schlegel testifies that Dr. Ghim was designated as the person in Dr. Jenson's

laboratory who would be performing the experiments with respect to recombinant production of L1 proteins and testing thereof. (SX 2068, ¶ 8). Dr. Ghim testifies, and her notebooks confirm, that she began work on the project to express full length and truncated HPV-1 L1 proteins. (SX 2073, ¶ 11, SX 2083, Bates Stamp Page 1658).

Regarding the alleged October 3, 1990 conception, Dr. Steinberg testifies:

> In my opinion, it was not unreasonable for Dr. Schlegel and Dr. Jenson to believe as of October 1990, that (i) an HPV L1 protein that had conformational epitopes of an L1 protein on intact HPV virions could be used in an immunoassay to detect antibodies produced in response to such intact virions or to generate antibodies for HPV serotyping in that as a result of common conformational epitopes, the recombinant protein and the intact virion would produce antibodies having such common conformational epitopes and such antibodies would bind to both the intact HPV virion and recombinant HPV L1 protein. It was also not unreasonable for them to believe that such a recombinant HPV L1 protein would be potentially usable as a vaccine in that as of such time it was generally believed that conformational epitopes of HPV virions were capable of producing neutralizing antibodies.

(SX 2076, ¶ 27).

Rose argues that Schlegel's October 3, 1990 work does not constitute a conception. (Paper No. 78, p. 25). According to Rose, Schlegel had no basis to reasonably predict that they could achieve the desired result, obtaining an HPV L1 protein having conformational epitopes. *Hitzeman v. Rutter*, 243 F.3d 1345, 1357-58, 58 USPQ2d 1161, 1170 (Fed. Cir. 2001).

Schlegel has provided sufficient and credible evidence that its inventors had a definite idea of an embodiment falling within the scope of the count. Yet, conception requires more than merely having a definite idea of a desired product. Conception requires that the idea be both complete and operative, such that there is a reasonable expectation for producing the desired invention. *Id.*

Schlegel fails to provide sufficient and credible evidence that the inventors possessed a complete and operative idea as of October 1990. In particular, we note that Dr. Steinberg's testimony, relied upon by Schlegel, does not state that obtaining an HPV L1 protein with conformational epitopes was reasonable but states that it was reasonable to expect that such a protein would be useful in an immunoassay. While it could be argued that Dr. Steinberg implicitly testifies that one of ordinary skill in the art could obtain the desired HPV L1 protein, such "implicit" testimony, at least in this case, fails to provide a specific and credible basis for concluding that it was reasonable to expect that one skilled in the art could obtain the desired HPV L1 protein having the stated conformational epitopes. *Rohm & Haas Co. v. Brotech Corp.*, 127 F.3d 1089, 1092, 44 USPQ2d 1459, 1462 (Fed. Cir. 1997) (Nothing in the rules or in jurisprudence requires trier of fact to credit unsupported or conclusory assertions).

Additionally, Dr. Schlegel testified as follows concerning the operability of an HPV-1 L1 having conformational epitopes:

Q. [Mr. Babcock]	I mean just concern in the scientific community or amongst your colleagues that part of the uncertainty dealing with whether or not the conformation would be correct or not is cellular factors may be involved that might inhibit the abilities of these proteins to mimic the native virus.
A. [Dr. Schlegel]	There were - - yeah, Bennett and I discussed those possibilities.
Q. [Mr. Babcock]	So until you did the work, it just wasn't known if those possibilities were going to be realities or not?
Mr. Olstein	Object.[6]

[6]Mr. Olstein's "objection" appears to be contrary to the guidelines for cross-examination. The purpose of the objection is not at all clear.

A. [Dr. Schlegel] Yes.

(SX 2109, page 114, lines 7 to 19).[7] We also note that Dr. Steinberg, who testified on behalf of Schlegel, testified that:

> In addition, one would have to perform such experiments without any reasonable probability that such experiments would eventually solve the problem in that there was nothing in art which would indicate that with respect to papillomaviruses, VLP's or L1 or L2 proteins which included conformational epitopes of the native virus could be produced. In my opinion, the art in this respect was unpredictable in that although L1 and L2 proteins had been produced by recombinant techniques, I am not aware of any investigator who produced recombinant L1 protein with "conformational epitopes" prior to July 1991 even though the art recognized that such a protein was desirable.

(SX 2001, ¶ 52).[8] Further, at oral hearing, Schlegel's counsel, Mr. Olstein, stated that until there was some demonstration that VLP's with conformational epitopes could be done recombinantly, there could be no conception. (Paper No. 98, p. 70, lines 6-14). We conclude that the state of the art was sufficiently uncertain such that some experimental indication was required to demonstrate that the recombinantly produced L1 protein had virion L1 conformational epitopes to establish a complete and operative idea of the invention as it was to be used in practice. We therefore hold that Schlegel failed to establish conception of an embodiment falling within the scope of the count by October 1990.

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[7]Schlegel is involved in the 104,772, 104,774 and 104,776 interferences and submitted identical exhibits and list of exhibits in each of the three interferences. While neither Schlegel nor Rose appears to have directed our attention to this particular piece of evidence in this interference (104,772), it nevertheless appears to confirm our underlying conclusion, that prior to conducting experimentation and testing, Schlegel's inventors lacked an operative method.

[8]Again, while neither Schlegel nor Rose relied upon this particular piece of evidence, Schlegel submitted this evidence into the 104,772 record. This evidence appears to support our holding that, prior to experimentation and testing, Schelgel's inventors lacked an operative method of obtaining an HPV L1 protein having conformational epitopes.

2. January 27, 1991

Schlegel argues that its grant application, dated January 27, 1991, serves as evidence of a conception of the invention. (Paper No. 74, p. 14). According to Schlegel, the grant application demonstrates that the inventors had constructed an *E. coli* expression vector including HPV-1 L1 DNA, and that the purpose of constructing such a vector was the production of an HPV-1 protein having conformational epitopes. (Schlegel Reply, Paper No. 81, p. 32).

The January 27, 1991 grant application states that the investigators:

> [I]ntend to define the external linear type-specific capsid antigens on the L1 protein of HPV1 for the purpose of investigating the relationship between the immune response and recurrences after treatment of productively infected HPV1-induced warts.

(Grant Application, SX 2086, page 8). The grant application corroborates Dr. Jenson's possession of an idea to construct HPV-1 L1 expression vectors "in an attempt assemble conformational capsid epitopes of HPV-1 *in vitro*" so as to prepare a vaccine to HPV-1. (Grant Application, SX 2086, pages 14-15). However, the grant application does not establish that the inventors had an operative idea of subject matter falling within the scope of the count. Specifically, the grant application, alone or in combination with Schlegel's October 3, 1990 evidence, does not provide a basis for concluding that Schlegel's inventors possessed an operative idea of an embodiment within the scope of the count.[9]

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[9]At oral hearing, Schlegel's counsel agreed that, in the '772 interference, Schlegel:

> . . . is forced at this point to in this particular interference, to argue that our conception and reduction to practice would have been the October 1991 date.

(Paper No. 98, p. 74, lines 3-19).

3. October 23, 1991

Schlegel alleges that its October 23, 1991 immunofluorescence assay constitutes a conception of an embodiment within the scope of the count, in particular claim 64. (Paper No. 74, page 22). According to Schlegel, the October 23, 1991 test was performed to demonstrate that a product expressed by transfected cos cells was an HPV-1 L1 protein that had conformational epitopes of the HPV L1 protein present on intact HPV-1 virions. (*Id.* at 17).

Rose argues that Schlegel's assays of October 23, 1991 and again in November 3, 1991, do not isolate the HPV L1 protein from the cos cells in which it was produced. Rose concludes that Schlegel failed to possess a reasonable expectation that it could produce an HPV L1 protein that specifically binds to conformational antibodies that react with an L1 protein expressed on the surface of an intact HPV virion. (Paper No. 78, p. 29).

Schlegel claim 64, which is part of the count, requires an isolated recombinantly produced HPV L1 protein. Schlegel does not characterize the HPV L1 protein that was tested on October 23, 1991 as having been isolated. Indeed, Schlegel acknowledges this in its argument that:

> To the extent that the work of October 23, 1991 does not establish an actual reduction to practice of the subject matter of Schlegel claims 1 and 64 in that the L1 protein was not "isolated," it does establish a conception.

(Paper No. 74, p. 22).

Schlegel argues that "it would only have involved routine skill to separate the L1 protein from the cellular matter and such procedures were well known in the art." (*Id.*). In support of this allegation, Schlegel relies upon the testimony of Drs. Jenson and Steinberg. (*Id.*). Dr. Jenson testifies that they intended to recover the expressed HPV-1 L1 protein expressed in the October 23, 1991 immunofluorescence assay and that several methods were known in the art

were available. (SX 2066, ¶ 24). Dr. Steinberg testifies that the recovery of the HPV-1 L1 protein would have been a routine matter. (SX 2076, ¶ 6). However, regarding the recovery of an HPV L1 with conformational epitopes, Dr. Steinberg has testified against Frazer that:

> (ii) The particle recovery conditions may have affected the conformational epitopes and, therefore, different recovery conditions would have to be explored, all without any guidance as to how, if at all, the recovery conditions affected conformation.

(SX 2001, ¶ 53).[10]

Schlegel fails to identify credible and specific evidence in its specification or elsewhere in the record that demonstrates one skilled in the art had a reasonable expectation that an HPV-1 L1 protein could be isolated from a cos cell without materially altering conformational epitopes present on the HPV-1 L1 protein. Further, Dr. Steinberg's contradictory testimony on this issue compromises the credibility of her statements that the HPV-1 L1 protein could be recovered as a routine matter. Based upon the record presented, we decline to credit Schlegel's alleged October 23, 1991 conception.

4. November 3, 1991

Schlegel argues that its immunofluorescence testing on November 3, 1991 is a corroborated conception of an embodiment within the scope of the count. (Paper No. 74, pages 23-24). Schlegel states that the testing was performed to demonstrate that cos cells transfected with HPV-1 L1 DNA expressed an HPV-1 L1 protein having conformational epitopes of L1 protein present on intact virions. (*Id.*). As with the October 23, 1991 testing, Schlegel did not

[10]While neither Schlegel nor Rose explicitly discuss this particular evidence, we note Dr. Steinberg's testimony is consistent with Schlegel's failure to present evidence establishing that one skilled in the art had a reasonable expectation of isolating HPV-1 L1 from cos cells without materially altering conformational epitopes on the HPV-1 L1 protein.

isolate the November 3, 1991 HPV-1 L1 protein. We conclude that, for the reasons provided above with respect to Schlegel's October 23, 1991 testing, Schlegel's November 3, 1991 testing likewise fails to evidence a conception of an operative embodiment falling within the scope of the count.

5. December 3, 1991

Schlegel alleges that its December 3, 1991 ELISA assay demonstrates a conception of an embodiment within the scope of the count. (Paper No. 74, pages 24-26). Dr. Ghim testifies that beginning in the last week of November 1991, she separated HPV-1 L1 protein from a lysate of cos cells that were transfected with a pSVL vector. (SX 2072, ¶ 118). In particular, Dr. Ghim testifies that she transfected the cos cells with her 1-9 HPV-1 L1/pSVL construct vector and with the 2-9 HPV-1 L2/pSVL construct vector. (*Id.* at ¶ 119). She also testifies that she labeled the cos cells with ^{35}S- methionine, lysed the cells and then centrifuged the lysate. (*Id.* at ¶ 120). The pellet material from the centrifuge was then suspended in a CsCl solution and subjected to a gradient centrifuge yielding nine fractions. (*Id.* at ¶ 132). Dr. Ghim testifies that she subjected the nine pellet fractions, as well as eight supernatant fractions, to an ELISA assay with diluted Pass #7 antiserum. (*Id.* at ¶ 134). Dr. Ghim testifies that fraction 7 of the pellet material was recognized by the Pass #7 antiserum and the testing demonstrates that she had isolated HPV-1 L1 protein that was recognized by a conformationally dependent HPV-1 L1 antibody. (*Id.* at ¶ 141). Dr. Steinberg testifies that the ELISA values reported in Dr. Ghim's notebook leads her to conclude that the value of 0.101 shown for pellet fraction 7 was more than two standard deviations above background level and that this demonstrates that pellet fraction 7 tested positive for HPV-1 L1 protein having conformational epitopes of L1 protein on an intact HPV-1 virions. (SX 2088, ¶¶ 96-97).

Dr. Jenson testifies that on or about December 3, 1991, he knew that Dr. Ghim had isolated recombinant HPV-1 L1 protein from cos cells. Dr. Jenson also testifies that on or about December 3, 1991 he knew that Dr. Ghim had demonstrated by ELISA assay testing that this protein had conformational epitopes of the L1 protein that is part of an intact HPV-1 virion. (SX 2066, ¶ 25).

Dr. Ghim's notebooks, in particular SX 2079, Bates Stamp Pages 300-303, are consistent with her testimony regarding the December 3, 1991 ELISA assay. Dr. Ghim testifies that her exhibits SX 2079-2084, are true and accurate copies of pages from her laboratory notebooks. (SX 2073, ¶ 8). Dr. Jenson testifies that exhibits SX 2079-2084 are in Dr. Ghim's handwriting and are taken from Dr. Ghim's notebooks. (SX 2066, ¶ 12). Dr. Wlazlo testifies that he worked in Dr. Jenson lab along with Dr. Ghim and that to the best of his knowledge, "Dr. Ghim performed the work recorded therein [SX 2079-2084] on or about the dates set forth in such exhibits" and that he observed the experiments described therein. (SX 2074, ¶ 50). On this basis, we hold that Schlegel has submitted sufficient and credible evidence to corroborate its December 3, 1991 ELISA testing.

Rose argues that Schlegel's December 3, 1991 ELISA assay is insufficient to constitute conception of an embodiment within the scope of the count. (Paper No. 78, p. 29). Rose identifies three alleged deficiencies:

1) Schlegel's ELISA assay employed "the deficient Pass #7 antiserum;"
2) The ELISA results "were only slightly above background level results;" and
3) "[T]he applied ELISA had not been evaluated sufficiently to determine if a significant observation had been made."

(*Id.*). These arguments, as well as Schlegel's response, are discussed below.

Rose states that Pass #7 antiserum has been shown to react with denatured major capsid protein of purified virions and that this suggests that Pass #7 reacts with linear epitopes. (*Id.* at ¶ 2, citing Sapp Declaration, RX 4222, ¶ 6). Schlegel's expert, Dr. Steinberg concedes that Pass # 7 antiserum is expected to contain antibodies that bind linear epitopes but explains that it is possible to dilute Pass #7 such that only polyclonal antibodies present therein bind detectably to an HPV1 L1 protein. (SX 2126, ¶ 4). According to Dr. Steinberg, Dr. Ghim's October 13, 1989 and October 29, 1991 testing demonstrates that Pass #7 could be diluted in a manner such that Pass #7 only binds detectably to conformational epitoes. (*Id.* at ¶ 5). Further, Dr. Steinberg testifies that the testing of the December 3, 1991 fractions was conducted using Pass #7, which was diluted such that "Pass #7 binds detectably only to conformational epitopes of HPV1 L1 protein." (SX 2126, ¶ 14). Based upon the evidence presented, we conclude that Dr. Ghim's December 3, 1991 ELISA testing on isolated recombinant HPV-1 L1 with diluted Pass #7 antiserum, where the diluted Pass #7 bound the recombinant HPV-1 L1, provided Drs. Schlegel and Jenson with a reasonable expectation that the isolated HPV-1 L1 protein was recognized by a conformationally dependent HPV-1 L1 antibody.

Rose, relying on testimony by Dr. Sapp, contends that the reported ELISA value of 0.101 was only slightly above background and that the results have not been reproduced. From this, Dr. Sapp concludes that it is unclear whether the reported ELISA assay value of 0.101 is a "significant observation."

Dr. Ghim testifies that the 0.101 result is above background and demonstrates that she had isolated HPV-1 L1 protein recognized by a conformationally dependent HPV-1 antibody. (SX 2072, ¶ 141). Further, Dr. Steinberg testifies that her evaluation of Dr. Ghim's December 3, 1991 ELISA values led her to conclude that the value of 0.101 was more than two standard

deviations above the background value and that an accepted practice in ELISA assays is that if an ELISA value is more than two standard deviations above the background value, then the ELISA value is a positive result. (SX 2088, ¶¶ 95-97). We credit the testimony of the non-inventors, Dr. Ghim and especially Dr. Steinberg, who indicates the quantitative basis for her opinion over the testimony of Dr. Sapp, who offers only his final conclusions. Based upon the evidence of record, we conclude that Dr. Ghim's ELISA assay testing reported on Bates Stamp Page 303 of SX 2079, demonstrates that Dr. Ghim obtained an isolated HPV-1 L1 protein that was recognized by a conformationally dependent HPV-1 antibody.

Rose also argues that Dr. Ghim's December 3, 1991 ELISA had not been evaluated sufficiently to determine if a significant observation had been made. In particular, Rose states that the ELISA may have contained a contaminating protein that bound the Pass #7 serum. (Paper No. 78, ¶ 3, relying upon Dr. Sapp Declaration, RX 4222, ¶ 9). As noted by Dr. Steinberg, Dr. Sapp's allegations regarding contamination are speculative. We find further that Dr. Sapp has not directed our attention to evidence that suggests that the December 3, 1991 ELISA contained contaminating material binding Pass #7. (SX 2126, ¶¶ 8-10).

We have considered Schlegel and Rose's evidence and arguments regarding Schlegel's alleged December 3, 1991 conception. Generally, we credit the testimony of Drs. Ghim, Wlazlo, Steinberg and Jenson as well as Dr. Ghim's supporting notebook pages. We do not credit the testimony of Dr. Sapp to the extent his testimony is inconsistent with their testimony. We conclude that Schlegel has provided sufficient and credible evidence of a corroborated conception no earlier than December 3, 1991. Specifically, no earlier than December 3, 1991, Senior Party Schlegel possessed a definite and permanent idea of a complete and operative embodiment falling within the scope of the count. On the present record, there is no need to establish the date more precisely.

In light of our determination that Schlegel conceived of an embodiment within the scope of the count no earlier than December 3, 1991 we do not address Schlegel's allegations regarding an alleged conception on March 16, 1992 and again on March 18, 1992. (Paper No. 74, pages 26-29). We note in passing that Rose concedes that Schlegel conceived of the invention on March 16, 1992. (Paper No. 78, p. 30).

C. Actual Reduction to Practice

Schlegel alleges five distinct actual reductions to practice. Whether an actual reduction to practice has been achieved is a question of law which is resolved on the basis of underlying facts. *Estee Lauder, Inc. v. L'Oreal, S.A.*, 129 F.3d 588, 592, 44 USPQ2d 1610, 1613 (Fed. Cir. 1997). Specifically, in an interference proceeding, a party seeking to establish an actual reduction to practice must satisfy a two-prong test: (1) the party constructed an embodiment that met every limitation of the interference count, and (2) the embodiment operated for its intended purpose. *Eaton*, 204 F.3d at 1097, 53 USPQ2d at 1698. As to the second prong, there must there be some recognition of successful testing prior to the critical date for an invention to be reduced to practice. Thus, an actual reduction to practice "does not occur until an inventor, or perhaps his agent, knows that the invention will work for its intended purpose." *Estee Lauder, Inc.*, 129 F.3d at 593, 44 USPQ2d at 1614.

Schlegel alleges that it actually reduced to practice subject matter within the scope of Schlegel claim 64. As discussed above, Schlegel claim 64 requires an "isolated" recombinantly produced HPV L1 protein. Schlegel's alleged first (October 23, 1991), second (November 3, 1991) and fifth (March 18, 1992) reductions to practice did not "isolate" the required HPV-1 L1 protein. Accordingly, Schlegel fails to demonstrate that is first, second and fifth reductions to practice involved an embodiment that met every requirement of that portion of the interference

count, Schlegel claim 64, that is alleged to have been reduced to practice. Schlegel's third (December 3, 1991) and fourth (March 16, 1992) alleged actual reductions to practice are discussed below.

1. December 3, 1991

The specifics of Schlegel's December 3, 1991 testing, and Rose's commentary thereon, have been discussed above with respect to conception. With respect to reduction to practice, Rose maintains that the use of Pass #7 antiserum fails to provide a satisfactory basis to conclude that Schlegel's HPV-1 L1 protein would bind specifically to conformational antibodies that react with an L1 protein on the surface of an intact HPV-1 virion. (Paper No. 78, pages 21-22).

Both Rose and Schlegel's experts, Dr. Sapp and Dr. Steinberg, agree that Figure 5 of the Pass article suggests that Pass #7 antiserum reacts with linear epitopes. (RX 4222, ¶ 7, SX 2107, 131:4-132:9 and 140:11-141:15). Dr. Steinberg testifies that the Pass #7 antiserum can be diluted to detect only the binding of conformational epitopes and states that Dr. Ghim's testing demonstrates that this is so.

While conception requires a reasonable expectation that the limitations of the count will actually be met, actual reduction to practice requires proof that every limitation has been met. We agree that Schlegel has demonstrated that one of ordinary skill in the art would have a reasonable *expectation* that diluted Pass #7 antiserum detectably binds to conformational, as opposed to linear, epitopes. Yet, we are not convinced that Dr. Ghim's Pass #7 antiserum testing is sufficient to rule out a plausible possibility that the Pass #7 antiserum bound linear, as opposed to conformational, epitopes on Schlegel's December 3, 1991 HPV-1 L1 protein. Specifically, one of ordinary skill in the art, aware that diluted Pass #7 bound a particular recombinant HPV-1 L1, would have required additional testing or information before knowing that the recombinant

HPV-1 L1 possessed conformational epitopes. *Estee Lauder*, 129 F.3d at 543, 44 USPQ2d at 1614.

2. March 16, 1992

Dr. Ghim testifies that on March 15 and 16, 1992, she conducted an immunoprecipitation assay on the expression product of cos cells transfected with the 1-9 vector, which contained an HPV-1 L1/pSVL construct. (SX 2072, ¶ 152). Specifically, Dr. Ghim states that she lysed transfected 1-9 cos cells, centrifuged the supernatant of the cell lysate, and reacted the recovered protein with monoclonal antibodies 336B6, D54G10 or 405D5 or Pass #7 antiserum. (*Id.* at ¶ 154). Dr. Ghim testifies that the March 15 and 16, 1992 immunoprecipitation assay demonstrates that monoclonal antibodies 336B6, D54G10 or 405D5 as well as the Pass #7 antiserum bound to HPV-1 L1 protein that had been expressed by the cos cells transfected with the HPV-1 L1/pSVL construct. (*Id.* at ¶ 155). Dr. Ghim identifies Bates Stamp Pages 330 and 331 of her notebook (SX 2079) as containing her notes regarding her March 15 and 16, 1992 immunoprecipitation assay. (SX 2072, ¶ 157).

Dr. Ghim further testifies that she ran an SDS-polyacrylamide gel to separate all the proteins bound to the Sepharose-Protein A beads resulting from the immunoprecipitation reaction on March 16, 1992. Dr. Ghim states that a photograph obtained from this assay appears in her notebook (SX 2079) at Bates Stamp Page 331, and is also shown at Figure 3 of Schlegel's involved application (SX 2023) and again as Figure 3 of Ghim et al. (SX 2087). (SX 2072, ¶ 159). According to Dr. Ghim, the immunoprecipitation gel shows that molecular weight bands corresponding to HPV-1 L1 protein were recognized by monoclonal antibodies 334B6, 339B6, D54G10 and 405D5 as well as Pass #7 antiserum. (*Id.*). Dr. Steinberg agrees with Dr. Ghim's analysis of the bands. (SX 2088, ¶ 111). Dr. Ghim concludes that she had obtained an isolated

HPV1 L1 protein that possessed the same conformational epitopes as that of intact HPV-1 L1 virions. (*Id.*).

Dr. Jenson testifies that:

> On or about March 16, 1992, I knew that Dr. Ghim (1) had expressed protein in cos cells that had been transfected with DNA encoding the L1 protein of HPV-1; (2) had isolated protein expression product from the cells by use of an antibody that bound to conformational epitopes of L1 protein present on intact HPV-1 virions; and (3) had demonstrated that the isolated expressed protein was an L1 protein of HPV-1 that had conformational epitopes of the L1 protein that is part of intact HPV-1 virions through the use of such antibodies and an immunoblot.

(SX 2066, ¶ 27). Dr. Jenson also testifies that, at such time, he understood and appreciated that the recombinant HPV L1 protein that had been expressed recombinantly by Dr. Ghim could be used in a diagnostic assay for detecting papillomavirus infection by the use of known immunoassay techniques. (*Id.* at ¶ 28).

Dr. Sapp, Rose's expert, reviewed Dr. Ghim's work and testifies that:

> This [Schlegel's March 16, 1992] immunoprecipitation assay followed by SDS-Page and autoradiography shows for the first time the presence of a 55 kDa L1 protein that can be extracted in a way that would allow the 405D5, D54G10, and 334B6 monoclonal antibodies and the Pass # 7 antiserum to bind and immunoprecipitate the recombinant L1 protein.

(RX 4222, ¶ 22).

Rose alleges that Schlegel's March 15 and 16, 1992 testing is insufficient to demonstrate an actual reduction to practice of a recombinantly-produced L1 major capsid protein that "mimics conformational neutralizing epitopes" on HPV. (Paper No. 78, p. 22). For this proposition, Rose cites Schlegel's involved specifications summary of the invention which states that "[a] recombinantly produced L1 major capsid protein which mimics conformational neutralizing epitopes on human and animal papilloma virions is provided." (SX 2023, p. 4, lines 2-3).

There is a heavy presumption in favor of the ordinary meaning of claim language. Although the written description may aid in the proper construction of a claim term, limitations, examples or embodiments appearing only therein may not be read into the claims. *Kraft Foods Inc. v. International Trading Co.*, 203 F.3d 1362, 1366, 53 USPQ2d 1814, 1817 (Fed. Cir. 2000). Thus, while a claim must be read in light of the specification, we will rarely import an unrecited, negative limitation into a claim. *Omega Engineering, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1323, 67 USPQ2d 1321, 1327 (Fed. Cir. 2003); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1325, 65 USPQ2d 1385, 1392-93 (Fed. Cir. 2003) ("Because the claims are best understood in light of the specification of which they are a part, however, courts must take extreme care when ascertaining the proper scope of the claims, lest they simultaneously import into the claims limitations that were unintended by the patentee."). This is especially true for applicants because an applicant, such as Schlegel, can resolve any ambiguity by amending the claim to contain the proposed limitations from the specification.

Rose fails to specifically explain why Schlegel claim 64, which is one alternative of Count 1, explicitly or implicitly requires an HPV L1 that mimics conformational neutralizing epitopes of HPV. Schlegel claim 64 merely requires that its HPV L1 protein specifically binds to conformational antibodies which react with an L1 protein expressed on the surface of an intact HPV virion and says nothing of "neutralizing" conformational epitopes. On this record, we do not construe Schlegel claim 64 as requiring an HPV L1 protein having conformational "neutralizing" epitopes.

Rose also argues that there is no assurance that Schlegel's HPV-1 L1 recombinant protein lacked mutations and was full length. Dr. Sapp testifies that Schlegel amplified its HPV-1 L1 coding sequence with *Thermus aquaticus* polymerase, which is allegedly known to introduce mutations into the sequences it amplifies. (RX 4222, ¶ 14). Dr. Sapp states that Dr. Ghim tested

several clones for mutations and that two clones were found to have mutations within the sites of the restriction enzymes used, which suggests to Dr. Sapp that Schlegel used conditions that caused mutations to occur. (*Id.*). Rose offers no express claim interpretation for Schlegel claim 64's use of the term "HPV L1 protein," but appears to imply that such a protein is limited to full length L1 protein that do not possess mutations.

Schlegel claim 64 is directed to an HPV L1 protein "comprising a protein which specifically binds to conformational antibodies which react with an L1 protein express on the surface of an intact HPV virion." Schlegel claim 64 does not explicitly exclude "mutant" HPV L1. Nor is Schlegel claim 64 expressly limited to a recombinantly produced protein having the "wild type" sequence.

Giving Schlegel claim 64 its broadest reasonable interpretation, we have interpreted Schlegel claim 64 as requiring, among other things, a protein that would be considered by one of ordinary skill in the art to be an HPV L1 protein. Dr. Ghim, Dr. Steinberg and Dr. Jenson have testified that the March 16, 1992 protein was an HPV-1 L1 protein. (SX 2072, ¶ 159, SX 2088, ¶ 111, and SX 2066, ¶ 27). Dr. Ghim's notebook also identifies the protein as an HPV-1 L1 protein. (SX 2079, Bates Stamp Page 330). Further, Rose and Dr. Sapp both refer to the March 16, 1992 protein as a recombinant HPV L1 protein. (Paper No. 78, p. 22 and RX 4222, ¶ 22). Accordingly, whether or not Schlegel's protein contains mutations does not raise sufficient doubt that Schlegel's protein is something other than a recombinant HPV-1 L1 protein that specifically binds to conformational epitopes that bind to an L1 protein expressed on the surface of an intact HPV virion.

Based upon the evidence of record, we conclude that Schlegel has presented sufficient and credible evidence that its March 16, 1992 recombinant HPV-1 L1 protein was tested and that the test results demonstrate that the protein binds to conformational epitopes that bind to an L1

protein expressed on the surface of an intact HPV virion. In so concluding, we credit the testimony of Dr. Ghim, Dr. Steinberg, Dr. Jenson as well as Dr. Ghim's notebooks and the corroborating testimony of Dr. Wlazlo. We do not credit the testimony of Dr. Sapp that Schlegel's March 16, 1992 protein was not an embodiment within the scope of the count as Dr. Sapp's testimony is not sufficiently supported by the evidence of record.

We note that Schlegel relies heavily on the activities of Dr. Ghim. Implicit in Schlegel's case is the allegation that Dr. Ghim's activities inure to the benefit of Schlegel. We note that:

> [I]nurement involves the claim that, as a matter of law, another person's activities should accrue to the benefit of the inventor. In order to establish inurement, an inventor must show, among other things, that the other person was working either explicitly or implicitly at the inventor's request.

Cooper, 154 F.3d at 1332, 47 USPQ2d at 1905 (Fed. Cir. 1998).

As mentioned above, Dr. Schlegel and Dr. Jenson testify that they agreed that Dr. Ghim was designated to perform the experiments with respect to the recombinant production of the L1 proteins and testing of the L1 protein. Consistent with Dr. Schlegel and Dr. Jenson's testimony, Dr. Ghim testifies that she was working in Dr. Jenson's laboratory and performed such experiments. Further, under cross-examination, Dr. Ghim testifies that she worked in Dr. Jenson's lab as a post-doctoral fellow, that all of her work was discussed in advance with Dr. Jenson and that she conducted her work accordingly. (See, e.g., SX 2105, p. 9, lines 6 to 17 and p. 11, line 17 to p. 12, line 3). Rose does not contest that Dr. Ghim's activities inure to the benefit of Schlegel. Based upon the evidence of record, we find that Schlegel has presented sufficient and credible evidence that Dr. Ghim was working in Dr. Jenson laboratory, and at Dr. Schlegel and Dr. Jenson's request she worked on producing and testing a recombinant L1 protein having conformational epitopes that are bound by conformational antibodies that react with an L1 protein expressed on the surface of an intact HPV virion and that she reported back to Drs. Schlegel and Jensen on a weekly basis.

D. Diligence

As set forth in 35 U.S.C. § 102(g):

> In determining priority of invention under this subsection, there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

Although our decisions in this interference do not require a resolution of Schlegel's diligence, our inquiry into the merits of Schlegel's arguments for conception and actual reduction to practice has led us to review the evidence of record to determine whether Schlegel exercised reasonable diligence from its established date of conception, December 3, 1991, until Schlegel's March 16, 1992 reduction to practice.

The reasonable diligence standard "balances the interest in rewarding and encouraging invention with the public's interest in the earliest possible disclosure of innovation." *Griffith v. Kanamaru*, 816 F.2d 624, 626, 2 USPQ2d 1361, 1362 (Fed. Cir. 1987). Indeed, underlying the reasonable diligence requirement is the public policy favoring the early disclosure of inventions. *Id.* Whether or not a party engaged in reasonable diligence is a question subject to the "rule of reason" as determined in the particular circumstances of each case. *Bey v. Kollonitsch*, 806 F.2d 1024, 1028 n.9, 231 USPQ 967, 970 n.9 (Fed. Cir. 1986).

The party chargeable with diligence must account for the entire period during which diligence is required, or provide a compelling reason to excuse the failure to take action. *Griffith v. Kanamaru,* 816 F.2d at 626, 2 USPQ2d at 1362. Testimonial evidence by the inventor or inventors must be adequately corroborated. If documentary evidence is relied on to establish reasonable diligence, it must show specific acts at specific times directed towards an actual or constructive reduction to practice of the invention of the count. *Naber v. Cricchi*, 567 F.2d 382, 386, 196 USPQ 294, 297-98 (CCPA 1977).

An inventor may demonstrate reasonable diligence based upon the inventor's own acts as well as others working explicitly or implicitly at the inventor's request. *Cooper v. Goldfarb*, 154 F.3d at 1331-32, 47 USPQ2d at 1904-05. For example, experiments conducted at the request of an inventor by another party may inure to the benefit of the inventor for purposes of establishing a reduction to practice. *Id.*

Dr. Ghim testifies that she worked continuously from October 1990 to June 1992 on a project for producing recombinant HPV L1 protein having conformational epitopes of an L1 protein that is part of an intact papillomavirus virion. (SX 2073, ¶ 3). Regarding Dr. Ghim's alleged diligence from the date of conception, December 3, 1991, to the date of actual reduction to practice, March 16, 1992, Dr. Ghim provides specific testimony describing her work in the laboratory for at least the following dates:

1991

December: 9, 12, 20, 28, 29

1992

January: 2, 5, 7, 8, 9, 10, 12, 13, 14-19, 23, 24, 25, 26, 28, 31
February: First and second weeks, 14-25, 26, 27
March: 1, 2, 3, 5, 6, 8, 9, 14, and 15

(Fourth Declaration of Dr. Ghim, SX 2073, ¶¶ 129-190). According to Dr. Ghim, her activities towards a reduction to practice was recorded in her notebooks, in particular, notebooks SX 2079 and SX 2081. (SX 2073, ¶¶ 8-10, 121).

Rose's Opposition Brief on the Issue of Priority (Paper No. 78) does not comment upon Schlegel's alleged diligence towards a reduction to practice between the dates of October 23, 1991 (Schlegel's First Alleged Reduction to Practice) and March 18, 1991 (Schlegel's Fifth Alleged Reduction to Practice), let alone from December 3, 1991 until March 16, 1991. Further, at oral hearing, Rose's counsel, Mr. Goldman, admitted that Rose did not contest Schlegel's

diligence for these dates. (Transcript of June 30, 2005 Oral Hearing, Paper No. 98, p. 84, line 13 to p. 85, line 4).

Based upon the record presented, we find that Schlegel has met its burden of proof to establish that it was diligent from the date of its conception, which is no earlier than December 3, 1991, until an actual reduction to practice on March 16, 1992.

VI. Conclusion

We have reviewed the parties arguments and evidence concerning Schlegel's case on priority of invention. Based upon this review we hold as follows:

It is held that:

Schlegel conceived of an embodiment within the scope of Count 1, the sole count in interference, its date of conception of no earlier than December 3, 1991.

Schlegel actually reduced to practice an embodiment falling within the scope of Count 1 no later than March 16, 1992.

Schlegel was reasonably diligent in its efforts to actually reduce to practice an embodiment falling within the scope of Count 1 from the date of its conception, which is no earlier than December 3, 1991 until it finally reduced the invention to practice, no later than March 16, 1992.

/ss/ Fred E. McKelvey
FRED E. McKELVEY, Senior
Administrative Patent Judge

/ss/ Sally Gardner Lane
SALLY GARDNER LANE
Administrative Patent Judge

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Appendix
Technical background for interferences 104,771 through 104,776

The following appendix is provided as an executive summary of the technical background underlying interferences 104,771 through 104,776. It is intended to be a convenient non-technical guide for those readers who are not familiar with the technology or the discussions in the Decisions on Preliminary Motions in the respective interferences. We have tried to keep it simple by not presenting the subtleties of the art or the points of disagreement. Those familiar with the art will recognize the oversimplifications. Moreover, we have not cited the record. Detailed findings of fact are set out throughout the decisions and opinions, which stand independently of this appendix. Although we believe this summary is accurate and consistent with the findings of fact and the conclusions drawn in the decisions and opinions, it is in no way a substitute for the detailed findings of fact.

Papillomaviruses

Papillomaviruses infect a wide variety of animals, typically giving rise to growths (warts) that may be painful or unsightly, but usually not malignant. The viruses are highly species and tissue specific. For example, the virus that gives rise to plantar warts on the soles of the feet of human beings (HPV-1) will not infect other human tissues, such as oral membranes, or any tissue of any non-human animal. By 1990, more than 50 distinct human papillomaviruses had been identified on the basis of differences among their DNA sequences, usually determined by DNA-matching ("hybridization") experiments.

Certain human papillomaviruses give rise to ano-genital warts, and certain of these viruses have been established as causative agents of cervical cancer. The type 16 human papillomavirus ("HPV-16") was the first virus implicated as a causative agent of cervical cancer. HPV-16 was identified by extracting viral DNA from an advanced cervical tumor and comparing

it to the DNA of other human papillomaviruses by hybridization experiments. Because it had a low degree of hybridization (*i.e.*, did not match) with other types, it was assigned a new type number, "16." Eventually, the DNA was sequenced, and samples were distributed to numerous laboratories around the world. This first isolated and sequenced HPV-16 DNA came to be called the "prototype HPV-16" DNA. The DNA of other HPV-16s and other papillomaviruses were also isolated and used in artificial genes to make virus proteins. Several other HPV types have also been implicated as giving rise to cervical cancer.

Papillomaviruses have a protein coat or shell made of two proteins, called "L1" and "L2." The L1 protein forms the outermost shell of the papillomavirus. The exact location of the L2 protein is not known, but it is thought to be in the interior of the shell.

Virus-like particles

When viruses infect cells, the viruses take over the cellular machinery and reproduce the viral DNA and all the proteins that make up the virus. The viral coat proteins often pack spontaneously around the viral DNA to form the mature viruses. Even in the absence of the viral DNA, the viral coat proteins may aggregate to form particles having the approximate size and shape of the native virus. Such particles, if they do not contain the viral DNA, are generally referred to as "virus-like particles."

We have not been directed to any evidence of reports of recombinantly-produced virus-like particles from papillomaviruses prior to the work at issue in these interferences.

Vaccines

The immune system can protect the body against invading viruses via antibodies to the outermost coat of the virus. Any given type of antibody will bind only to a specific site having a particular molecular shape or "conformation." Antibodies that bind to specific sites, called "epitopes," on the surface of an intact virus, are said to bind to "conformational epitopes." If the antibodies bind to all the receptor sites on the virus that the virus uses to bind to cells, receptor sites will be blocked, and the ability of the virus to infect cells will be neutralized.

Antibodies are made by specialized cells. A given antibody-making cell makes antibodies that recognize only one specific epitope. When the individual is exposed to a particular virus, the cells that make the antibodies that recognize the protein coat of that virus will be stimulated to make more antibodies, and they will remember that virus. Upon future exposure to that virus, the individual's immune system will be prepared to make large quantities of those antibodies.

Vaccines work by priming the immune system to produce large numbers of neutralizing antibodies to particular viruses. In some cases, the patient can be exposed to a killed or weakened strain of the virus rather than the active virus itself. The process of killing or weakening the virus, however, may change the exposed surface of the virus so much that few antibodies to the active virus are activated. It is also possible that the killed or weakened virus may be re-activated, leading to infection and disease rather than immunization.

A gene is a DNA molecule that carries the genetic code that instructs the cell how to make a particular protein. Genetic engineering using so-called "recombinant" techniques involves "recombining" a foreign gene with the genes of a host cell. Then the machinery of the host cell is harnessed to make the protein coded for by the foreign gene. That protein can be made in large quantities, isolated, and purified. These recombinant techniques brought hopes

that the coat proteins of viruses could be produced in large quantities, cheaply, easily, and completely free of viral DNA.

If the recombinant viral coat protein had the same conformational epitopes as the proteins in the native virus, it might serve as a vaccine. Because the protein would not be subjected to the process of weakening or killing the virus, it might be more effective at priming the immune system to make antibodies against the virus than vaccines made from viruses. Moreover, a vaccine made from such proteins would carry no risk of inducing the viral disease, such as cervical cancer. Given the tendency of many viral coat proteins to form virus-like particles, the virus-like particles, if they had the conformational epitopes of the native virus, could also serve as vaccines.

Only a couple of reports of vaccines based on recombinantly produced virus-like particles appear in the record as "prior art" to the applications involved in these interferences. The most prominent example in the record of a prior-art recombinant viral coat protein vaccine is that for hepatitis-B, which was the subject of the interference reported in *Hitzeman v. Rutter*, 243 F.3d 1345, 58 USPQ2d 1161 (Fed. Cir. 2001).

Diagnostic reagents

In addition to uses as vaccines, recombinantly produced viral coat proteins having the conformational epitopes of the L1 protein of the native virus could also be used as diagnostic reagents to determine whether an individual had been exposed to a particular type of papillomavirus. Serum from the individual would be checked for the presence of antibodies to the papillomavirus by looking for reaction with the recombinant protein. A significant degree of reaction between the recombinant protein and the serum would indicate that the serum contained

an elevated level of antibodies to the papillomavirus, indicating exposure of the patient to that virus.

Proofs of the parties

In their proofs for conception and actual reduction to practice, the parties have attempted to show why their laboratory work at various stages provided sufficient evidence that various limitations of the Counts, particularly the existence of conformational epitopes, had been demonstrated. The parties mutually have challenged the sufficiency of proof each has offered for conception and actual reduction to practice of the counts in the various interferences. In briefest outline, the positions of the parties follow.

Frazer discloses, in its Australian, PCT, and involved applications, particles made from the L1 and L2 proteins of an HPV-16 virus. These particles are significantly smaller (average diameter reported to be 35–40 nm) than all known papillomaviruses (diameters reported to be 50–60 nm). These particles are also irregularly shaped, rather than essentially spherical or icosahedral. Frazer presents no credible evidence that indicates that these particles have conformational epitopes of the native HPV-16 virus. Instead, Frazer maintains that such conformational epitopes are inherently present in the particles it produced. Frazer's position has not been accepted, and it has been denied the benefit for priority of its Australian application. (In contrast, the particles from other papillomaviruses disclosed in Frazer's PCT application and in its involved application are about 50 nm in diameter and regularly shaped. Motions by Frazer's opponents that the disclosures of these particles failed as constructive reductions to practice of the Count were unsuccessful in the preliminary motions phase. Thus, Frazer was accorded the benefit for priority of its PCT application.)

Schlegel discloses L1 protein from HPV-1, together with experimental evidence that it maintains shows that the L1 protein has the conformational epitopes of the L1 protein in the native virion. Schlegel reports, however, that it looked for but did not find evidence indicating the presence of virus-like particles in its L1 protein preparations.

Lowy discloses virus-like particles and experimental evidence that it maintains shows that the virus-like particles it reports have at least one conformational epitope of the native virus and are capable of inducing neutralizing antibodies to the native virus.

Rose discloses virus-like particles and experimental evidence that it maintains shows that the virus-like particles it reports are conformationally correct and are recognized by antibodies from patients, including human patients, infected by the corresponding virus.

More detailed summaries of the technology and of particular technical issues involved in individual interferences may be found in the various decisions on preliminary motions and decisions on priority dates. We emphasize again that this summary is not a substitute for formal findings of fact in the decisions on priority dates.

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